

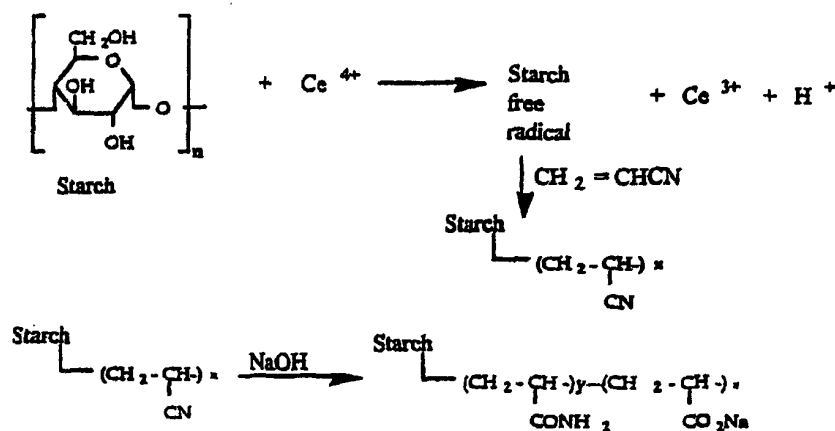
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(21) International Application Number: PCT/EP00/01107 (22) International Filing Date: 11 February 2000 (11.02.00) (30) Priority Data: 60/119,849 12 February 1999 (12.02.99) US (71) Applicants (for all designated States except US): UNIVERSITEIT GENT [BE/BE]; St. Pietersnieuwstraat 25, B-9000 Gent (BE). BEN-GURION UNIVERSITY OF THE NEGEV RESEARCH AND DEVELOPMENT AUTHORITY [IL/IL]; P.O. Box 653, 84105 Beer Sheva (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): REMON, Jean, Paul [BE/BE]; John Youngstraat 11, B-9090 Melle (BE). GERESH, Shimona [IL/IL]; 27 Tapuz Str., 84965 Omer (IL). KOST, Joseph [IL/IL]; 54 Hashita Str., 84965 Omer (IL). (74) Agents: BIRD, William, Edward et al.; Bird Goën, Termestraat 1, B-3020 Winksele (BE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: A BIOCOMPATIBLE ADHESIVE SYSTEM AND A BIOADHESIVE DRUG DELIVERY SYSTEM WITH CONTROL-LABLE RELEASE



(57) Abstract

Bioadhesives and controlled release drug delivery systems were prepared from a series of starches grafted with acrylic monomers by two initiation methods: chemical and radiation. In general, the grafted starches prepared by chemical initiation with a $\text{Ce}^{4+}/\text{Ce}^{3+}$ redox system showed a lower bioadhesion and released the model drugs in relatively shorter. These materials can be characterized by measuring

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A BIOCOMPATIBLE ADHESIVE SYSTEM AND A BIOADHESIVE DRUG DELIVERY SYSTEM WITH CONTROLLABLE RELEASE

The present invention relates to a biocompatible adhesive system and a bioadhesive drug
5 delivery system with controlled release. The bioadhesive system in accordance with the
present invention is particularly useful in a skin or mucosal drug delivery system with
which the release time of the drug may be designed appropriately for the application, and it
can also be applied as an oral delivery system for an active component, e.g. a drug, for
sustained release of the active component.

10

TECHNICAL BACKGROUND

Conventional buccal bioadhesives used as drug delivery systems are often based on
hydrogels because, when hydrated, these compounds adhere to the mucosa and withstand
the effects of salivation, swallowing and even physical movements. The molecular
15 characteristics for obtaining a good bioadhesion appear to be strong H-binding groups
such as -COOH or -OH and high anionic charges.

Polyacrylic acid is known as one candidate polymer for mucoadhesives and
combinations of hydroxypropylmethylcellulose, hydroxypropylcellulose, and sodium
carboxymethylcellulose and starch with polyacrylic acid such as polycarbophil or Carbopol
20 934 are known. However, the potential irritation associated with the use of polyacrylic
acid in buccal bioadhesives has often been disregarded. In practice, these conventional
systems have severe limitations because of their irritation potential. A mixture of starches
and polyacrylic acid has been shown to yield a less irritant bioadhesive matrix.

A mucoadhesive or cutaneous adhesive drug delivery system should preferably
25 allow adaption to specific targets, to specific active components and/or release times.
Successful drug application requires not only a system which is capable of delivering a
specific drug but also a controllable release of that drug. A complete mucoadhesive or
cutaneous adhesive delivery system should preferably be designable, i.e. the system should
have sufficient design parameters that a range of release times can be predetermined even
30 for the same drug. Further, the release should preferably be non-Fickian, i.e. not purely
dictated by simple diffusion of the drug. The rate of Fickian diffusion depends on the
difference in drug concentration between the drug delivery system and the target, hence,

the rate is high at the start and then reduces rapidly. It would be preferred if the rate of delivery were more constant.

A mucoadhesive or cutaneous adhesive should also preferably be preparable in a variety of suitable physical forms, e.g. as tablets, monolayered or multilayered patches, as
5 beads, pellets or microspheres for inclusion in other systems, and/or in bulk layers suitable for external or internal application.

US 5,707,644 describes small particle compositions for intranasal drug delivery including a plurality of bioadhesive microspheres (at least 90% of which have a diameter between 0.1 micron and 10 micron) and an active drug associated with each microsphere.
10 Possible biocompatible materials suggested for preparation of the bioadhesive microspheres are starch or dextran derivatives including grafted starches. No examples of grafted starches are given.

A biodegradable plastic and methods of grafting methyl acrylate to starch using cerium ammonium nitrate are known from the article "A new biodegradable plastic made
15 from starch graft poly(methyl acrylate) copolymer", by Dennenberg et al. Journal of Applied Polymer Science, vol. 22, pages 459 to 465 (1978).

Methods of grafting starch to acrylic acid are known from "Grafting acrylic acid to starch by preirradiation", Reyes et alia, Journal of Polymer Science, vol. 23, pages 401 to 408, 1968.

20 A review of methods of grafting starch is provided in Chapter 10 "Grafted starches" of the book by O. B. Wurzburg, CRC Press Boca Raton, 1986, entitled "Modified starches: Properties and uses".

A known use of acrylic-starch grafted copolymers is as superabsorbent materials, e.g. saponified gelatinised starch-polyacrylonitrile graft polymers as known from US
25 3,935,099 and saponified starch-acrylonitrile graft copolymers are known for use in sustained release dosage forms from US 4,713,237. Starch-polyacrylonitrile graft polymers have found use as moisture absorbing polymers in methods for promoting growth of seeds, e.g. US 5,317,834 and in insecticidal delivery systems as known from US 4,818,534.

An object of the present invention is to provide a bioadhesive, preferably a
30 mucoadhesive or a cutaneous adhesive, more preferably a buccal adhesive which is substantially non-toxic and, in particular, has a reduced irritation potential.

Another object of the present invention is to provide a bioadhesive comprising

nontoxic compounds and allowing incorporation of an active component such as a drug while not inhibiting its release.

It is also an object of the present invention to provide a biocompatible adhesive system.

5 A further object of the present invention is to provide a bioadhesive which may be used for adhering to any human or animal internal or external mucosa or skin or to plants or trees.

In particular, it is an object of the present invention to provide a bioadhesive whose adhesive property is resistant to saliva, other mucosal fluids or other forms of water as
10 well as to physical movement of the target substrate, in particular, to swallowing.

Still a further object of the present invention is to prepare a bioadhesive which allows controlled release of active compounds such as chemicals, medical drugs or active compounds, cosmetics.

Another object of the present invention is to provide a bioadhesive system which is
15 designable, i.e. has sufficient design parameters that release times may be adapted to the application, the active component to be delivered, and the required release time of the active component.

SUMMARY OF THE INVENTION

20 The present invention may provide a bioadhesive agent wherein the bioadhesive property of the agent is provided mainly or substantially by a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative. The present invention may provide a bioadhesive agent wherein the bioadhesive property of the agent is provided mainly or substantially by
25 a copolymer of a poly- α -glucoside and at least an α , β -ethylenically unsaturated monocarboxylic acid or acid derivative. Simultaneously, cross-linking may be performed by high energy radiation. The present invention also includes a bioadhesive system comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically
30 unsaturated monocarboxylic acid or acid derivative. The present invention also includes a bioadhesive system comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of copolymer of a poly- α -glucoside and at least an α , β -ethylenically

unsaturated monocarboxylic acid or acid derivative. The bioadhesive agent may include other solid or liquid components. The other component may be releasable from the bioadhesive agent such as, for instance, an active component. No limits are anticipated on the active component other than it should be preferably incorporatable into the bioadhesive agent. It may be, for instance, a therapeutic substance or a pharmaceutically active agent such as a drug, a non-therapeutic substance such as a cosmetic substance, a local or general anaesthetic or pain killer, e.g. lidocaineTM or novocaineTM or an opiate, a vaccine, an antigen, a microorganism, a sterilizing substance, a contraceptive composition, a protein or peptide such as insulin, an insecticide, a herbicide, a hormone such as a growth hormone or a seed germination hormone, a steroid, a toxin, a marker substance, e.g. a radioactively labeled compound. Alternatively or additionally, another component of the bioadhesive agent may be an excipient such as a binder.

The present invention also includes an adhesive material for animal or human mucosa, skin, body parts or tissue or vegetable or plant parts or tissue, the adhesive material including a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative. The present invention also includes the use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative as a bioadhesive agent. Both therapeutic and non-therapeutic, e.g. cosmetic or pest control, applications are included within the scope of the present invention. The present invention also includes the use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative in the manufacture of a bioadhesive agent for use in compositions for therapeutic or non-therapeutic, e.g. cosmetic or pest control purposes. The graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative in accordance with the present invention also may exhibit swelling properties and can take up and controllably release an active component, such as a drug. The present invention also includes a controlled release active component delivery vehicle comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative. The

active component may be incorporated into the bioadhesive agent. The present invention also includes the use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative as a bioadhesive agent in a controlled release active component delivery vehicle. Both

5 therapeutic and non-therapeutic applications are included within the scope of the present invention. The present invention also includes the use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative as a bioadhesive agent in the manufacture of a controlled release active component delivery vehicle. Controlled release includes

10 prolonged or sustained release as well as rapid release. In particular, the release time may be designed by the appropriate adaption of the bioadhesive agent. No limits are anticipated on the active component other than it should be preferably incorporatable into the bioadhesive agent. It may be, for instance, a therapeutic substance or a pharmaceutically active agent such as a drug, a non-therapeutic substance such as a cosmetic substance, a

15 local or general anaesthetic or pain killer, e.g. lidocaineTM or novocaineTM or an opiate, a vaccine, an antigen, a microorganism, a sterilizing substance, a contraceptive composition, a protein or peptide such as insulin, an insecticide, a herbicide, a hormone such as a growth hormone or a seed germination hormone, a steroid, a toxin, a marker substance, e.g. a radioactively labeled compound. A non-limiting list of active components, e.g. drugs, for

20 use in the bioadhesive compositions according to the present invention includes hydrochlorothiazide, acetazolamide, acetylsalicylic acid, allopurinol, alprenolol, amiloride, antiarrhythmics, antibiotics, antidiabetics, antiepileptics, anticoagulants, antimycotics, atenolol, bendroflumethiazide, benzbromarone, benzthiazide, betamethasone, ester thereof, bronchodilators, buphenine, bupranolol, chemotherapeutics, chlordiazepoxide,

25 chloroquine, chlorothiazide, chlorpromazine, chlortalidone, clenbuterol, clomipramine, clonidine, co-dergocrine, cortisone, ester thereof, dexamethasone, ester thereof, dextropropoxyphene, diazepam, diazoxide, diclofenac, diclofenamide, digitalisglycoside, dihydralazine, dihydroergotamine, diltiazem, iron salt, ergotamine, ethacrynic acid, ethinylestradiol, ethoxzolamide, fenoterol, fludrocortisone, ester thereof, fluphenazine,

30 furorosemide, gallopamil, guanethidine, hormone, hydrochlorothiazide, hydrocortisone, ester thereof, hydroflumethiazide, immunosuppressives, ibuprofen, imipramine, indomethacine, coronatherapeutics, levodopa, salt of lithium, salt of magnesium,

medroxyprogesteron acetate, menadione, methaqualone, 8-methoxypsoralen, methylclothiazide, methyl dopa, methylprednisolone, methyltestosterone, methylthiouracil, methylxanthine, metipranolol, molsidomine, morphine, naproxen, nicergoline, nifedipine, norfenefrine, oxyphenbutazone, papaverine, parmathasone, ester thereof, pentobarbital, perphenazine, phenobarbital, phenylbutazone, phytomenadione, pirenzepine, polythiazide, prazosine, prednisolone, ester thereof, prednisone, ester thereof, probenecid, propranolol, propylthiouracil, rescinamine, reserpine, secbutabarbital, secobarbital, spironolactone, sulfasalazine, sulfonamide, thioridazine, triamcinolon, ester thereof, triamteren, trichlormethiazide, trifluoperazine, trifluopromazine, tuberculostatic, verapamil, virustatics, zytostatics, bromocriptine, bromopride, carbidopa, carbocromen, quinine, chlorprothixene, cimetidine, clofibrat, cyclizine, desipramine, disulfiram, domperidone, doxepine, fenbufen, flufenamine acid, flunarizine, gemfibrocil, haloperidol, ketoprofen, labetalol, lorazepam, mefenamine acid, melperone, metoclopramide, nortriptyline, noscapine, oxprenolol, oxymetholone, pentazocine, pethidine, stanozolol, sulindac, sulpiride, tiotixen.

By bioadhesive agent is meant a component which provides bioadhesive properties to a composition in which it is included rather than, for instance, an excipient in a bioadhesive composition. Bioadhesive properties means that adhesive properties are developed on contact with animal or human mucosa, skin or body tissue or vegetable or plant tissues, i.e. the bioadhesive develops adhesive properties when used as a mucosal or transdermal adhesive, that is on those living surfaces which include some water or an aqueous solution. Pressure may need to be applied to the bioadhesive agent when applied to the animal or human mucosa, skin or body tissue or vegetable or plant tissue to activate the adhesive properties. In particular, a bioadhesive agent in accordance with the present invention may provide a biocompatible, hydrophilic adhesive which may be pressure sensitive. The adhesive action of a bioadhesive agent in accordance with the present invention may be based on the interpenetration of the chains of the graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative or the poly- α -glucoside moiety of the graft copolymer in accordance with the present invention with polymeric chains formed on the surface of the substrate, e.g. glycoprotein chains of the oral mucosa. In one aspect a bioadhesive agent in accordance with the present invention may be described generally as providing an interpenetrating bioadhesive. A bioadhesive agent in accordance with the present invention does not necessarily develop adhesive

properties when contacted with bulk water or a bulk aqueous solution (i.e. without a suitable biological substrate as well). In some aspects of the present invention it is preferred that the bioadhesive agent in accordance with the present invention does not form an adhesive surface when in contact with bulk water. Preferred embodiments of the present invention form non-adhesive gels when contacted with bulk water or aqueous solutions, e.g. on contact with bulk saliva rather than on pressure contact with a salival film on a mucosal surface such as the buccal mucosa. The differentiated behaviour with respect to bulk and surface film water and aqueous solutions is especially of advantage when the bioadhesive agent in accordance with the present invention is used as an active component delivery system, e.g. as a controlled release drug delivery buccal adhesive. The bioadhesive system in accordance with the present invention is preferably deliverable in a non-adhesive and dry form for instance, as a tablet, and the adhesive properties are only activated when the system is placed in contact with mucosa, body tissue, skin, vegetable or plant tissue or a similar surface. The bioadhesive agent in accordance with the present invention is preferably biocompatible, in particular, non-cytotoxic.

The term graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative as used herein means any such monomer which can be grafted onto a poly- α -glucoside under suitable conditions such as free radical initiation or high energy radiation may include: monocarboxylic acids such as acrylic acid, methacrylic acid, ethacrylic acid, alkenoic acid, acrylic acid being preferred; esters of the said acids with an alcohol or aminoalcohol having from 1 to 18 carbon atoms such as alkyl acrylates and methacrylates, the alkyl group being selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, hexyl, n-octyl, ethylhexyl, nonyl, dodecyl, stearyl, and possibly being substituted with hydroxy groups (e.g. hydroxyethyl) or halo- atoms such as fluoro, dimethylaminoethyl acrylate and methacrylate, and the like; acrylonitrile, methacrylonitrile; and alkaline or alkaline earth salts, e.g. sodium, potassium, calcium of the above acids. For example, other comonomers may be included from the above with the monocarboxylic monomer during the grafting to a poly- α -glucoside, e.g. esters of acrylic or methacrylic acids and derivatives such as 2-dimethylaminoethyl methacrylate.

The poly- α -glucoside may be any chemically or physically modified starch or oligosaccharides, in particular, any poly- α 1,4-glucoside or poly- α 1,6-glucoside. Poly- α 1,6-glucoside includes dextran. Poly- α 1,4-glucosides include leguminous, cereal or

tuber starches or a hydrolysate of such a starch. A non-limiting list of starch sources includes corn, wheat, barley, oats, pea, waxy maize, arrowroot, sorghum, rice, waxy sorghum, waxy rice, soya, potato. Further, the poly- α -glucoside may include branched or unbranched polymaltoses such as amylopectin or amylose or thinned starches (hydrolysates of starch) including maltodextrose. The graft copolymer in accordance with the present invention may be or may not be at least partly saponified. The graft copolymer in accordance with the present invention is preferably not water soluble.

Without being limited by theory, it is believed that the poly- α -glucoside forms the backbone, whereas the moiety derived from the graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative (hereinafter named "acrylic moiety" for purposes of simplification) forms the branches of the grafted copolymer. It is included within the present invention if the grafted acrylic moiety, may be partly ionised. In particular, it is preferred, e.g. when used in a controlled release drug delivery system, if the side chains, i.e. the grafted acrylic moiety, include salts, preferably monovalent or divalent salts, e.g. calcium, magnesium, or sodium salts of acrylic acid. Further, preferred embodiments of the present invention include acrylic-poly- α -glucoside grafted copolymers in which the graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative side chains are cross-linked among themselves. The present invention includes a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative which forms a three-dimensional cross-linked matrix or gel which exhibits bioadhesive properties, i.e. has inherent bioadhesive properties without addition of other components.

The present invention includes graft copolymers manufacturable by at least two methods as well as the methods themselves: free radical or chemical initiation and initiation by irradiation, the choice of the method depending, in part, on the particular monomer or combination of monomers to be polymerized. In particular, graft copolymers of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative and methods of their manufacture are included within the present invention based on at least two initiation methods 1) gamma irradiation, e.g. from a ^{60}Co source and 2) free radical initiation such as by means of ceric ammonium nitrate, peroxides, hydroperoxides, diazo compounds. Particularly preferred are irradiation initiated poly- α -glucoside graft copolymers. Particularly preferred are copolymers which

are manufactured by irradiating mixtures of a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative and a poly- α -glucoside, i.e. by so-called simultaneous irradiation, but the present invention also includes preirradiation of a poly- α -glucoside to form free radicals followed by addition of the acrylic monomer as well as chemical initiation. The poly- α -glucoside such as starch may be gelatinised before grafting to the acrylic monomer or granules may be grafted directly. Various parameters such as irradiation times and the weight percentages of the poly- α -glucoside and/or the graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative monomer may be adjusted to provide selectable adhesive properties and/or selectable release rates for the desired active compounds to be included in the bioadhesive agent in accordance with the present invention. The graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative in accordance with the present invention may be characterised by physicochemical methods and the size and nature of the acrylic moiety grafted to the poly- α -glucoside. For example, grafted copolymers may be characterized by FT-IR spectroscopy and by ^{13}C -NMR spectroscopy, from which the molecular weights of the acrylic moiety grafted onto the a poly- α -glucoside may be determined. Conventional molecular weights (average number) of the acrylic moiety obtainable by the above-referenced initiation methods lie in the range 5,000 to 100,000, preferably from 10,000 to 50,000. Variation of the parameters of the grafting process may be used to design suitable controlled release bioadhesives in which both the release time of the active component, e.g. a drug, and the extent of bioadhesion may be tailored to specific applications. In particular, the kinetics of the controlled release of model drugs (sodium salicylate and theophylline) have shown that the release behavior of the drugs from the controlled release system in accordance with the present invention is non-Fickian.

The present invention also includes a process for manufacturing a bioadhesive agent by the steps of:

- a) graft copolymerising a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative;
- b) mixing the graft copolymer with an additional substance.

The present invention also includes a process for manufacturing a bioadhesive agent by the steps of:

- a) copolymerising a poly- α -glucoside and at least a copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative;
- b) mixing the graft copolymer with an additional substance. The colymerisation is preferably carried out in the presence of high energy radiation which also induces cross-linking.

The additional substance may be releasable from the bioadhesive agent such as an active component, for instance. No limits are anticipated on the active component other than it should be preferably incorporatable into the bioadhesive agent, for example by means of encapsulation or microencapsulation. It may be, for instance, a therapeutic substance such as a drug, a vaccine, an antigen, a microorganism, a non-therapeutic substance such as a cosmetic substance, a local or general anaesthetic or pain killer or an opiate, a sterilising substance, a contraceptive composition, a protein such as insulin, an insecticide, a herbicide, a hormone such as a growth hormone or a seed germination hormone, a steroid, a toxin, a marker substance, e.g. a radioactive compound.

Alternatively, the additional substance may be an excipient such as a binder.

The present invention also includes a method of adhering a material to animal or human mucosa, skin, body tissue or vegetable or plant tissue using a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of an acrylic-poly- α -glucoside graft copolymer. Both therapeutic and non-therapeutic applications are included within the scope of the present invention.

The present invention also includes a method of fabricating a controlled release active component delivery vehicle comprising the steps of

- a) forming the delivery vehicle from at least a bioadhesive agent by graft copolymerising a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative;
- b) including an active component in the delivery vehicle.

The present invention also includes a method of fabricating a controlled release active component delivery vehicle comprising the steps of

- a) forming the delivery vehicle from at least a bioadhesive agent by copolymerising a poly- α -glucoside and at least a copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative;
- b) including an active component in the delivery vehicle.

The active component may be incorporated into the bioadhesive agent.

The dependent claims define individually and separately further embodiments of the present invention. The present invention will now be described with reference to the following drawings.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a reaction scheme showing ceric ammonium nitrate (CAN) initiated graft polymerization of acrylonitrile (AN) onto starch (top) and alkaline hydrolysis of the starch-g-polyacrylonitrile (bottom) in accordance with embodiments of the present invention.

10 Fig. 2 is an FT-IR spectrum of starch-g-polyacrylonitrile (1 : 1.5) in accordance with an embodiment of the present invention.

Fig. 3 is an FT-IR spectrum of starch-g-polyacrylic acid (1 : 1.5) in accordance with an embodiment of the present invention.

15 Fig. 4 is a general representation of a scheme of acid hydrolysis of starch-g-polyacrylonitrile.

Fig. 5 is a graph showing swelling (swollen weight/dry weight) of starch-g-polyacrylic acid in accordance with an embodiment of the present invention in water and different buffers at various pH values.

20 Fig. 6 shows the effect of irradiation time on the kinetics of release of salicylic acid from potato starch-g-acrylic acid (1:2.5) in accordance with an embodiment of the present invention.

Fig. 7 shows the effect of irradiation time on the kinetics of release of theophylline from potato starch-g-acrylic acid (1:2.5) in accordance with an embodiment of the present invention.

25 Fig. 8 shows the effect of irradiation time of grafting on the drug release rate of a grafted starch in accordance with an embodiment of the present invention.

Fig. 9 shows release of salicylic acid from a potato starch-g-acrylic acid copolymer in accordance with an embodiment of the present invention.

30 Fig. 10 shows release of salicylic acid from a rice starch-g-acrylic acid copolymer in accordance with an embodiment of the present invention.

Fig. 11 shows release of salicylic acid from a grafted potato starch (5 wt.%) in accordance with an embodiment of the present invention using two different amounts of

acrylic acid.

Fig. 12 shows release of salicylic acid from graft copolymers of acrylic acid with various amounts of potato starch in accordance with an embodiment of the present invention.

5 Fig. 13 shows the rate of release of theophylline from graft copolymers obtained from grafting starch with acrylic acid in weight ratios of 1:12.5; 1:25, and 1:37.5 in accordance with embodiments of the present invention.

Fig. 14 shows release of theophylline from a dry piece of grafted starch (1) and from a tablet (2) manufactured in accordance with embodiments of the present invention.

10 Fig. 15 shows the release of theophylline from tablets (without binder) of grafted copolymers of two different starches with acrylic acid in accordance with embodiments of the present invention.

Fig. 16 shows the release of theophylline from tablets (with binder) of grafted copolymers of two different starches with acrylic acid in accordance with embodiments of
15 the present invention.

Fig. 17 shows release of theophylline from starches grafted with partially neutralized acrylic acid (dissolution medium at pH 5) in accordance with an embodiment of the present invention.

Fig. 18 shows release of theophylline from various starches grafted with acrylic acid partially neutralized with MgO (dissolution medium at pH 3) in accordance with an
20 embodiment of the present invention.

Fig. 19 shows release of theophylline from various starches grafted with acrylic acid partially neutralized with CaO (dissolution medium at pH 7) in accordance with an embodiment of the present invention.

25 Fig. 20 shows release of theophylline from malto-dextrose (#1924) grafted with partially neutralized acrylic acid (dissolution medium at pH 5) in accordance with an embodiment of the present invention.

Fig. 21 shows release of theophylline from maltodextrose (#1910) grafted with partially neutralized acrylic acid (dissolution medium at pH 5) in accordance with an
30 embodiment of the present invention.

Fig. 22 shows release rates of salicylic acid (SA) and theophylline as model drugs from tablets of grafted rice starch (prepared with a starch:acrylic acid ratio of 1:5 in the

presence of Ca^{2+}) in accordance with an embodiment of the present invention.

Fig. 23 shows the release rate of increasing concentrations of theophylline from tablets of grafted corn starch (prepared with a starch:acrylic acid ratio of 1:5 in the presence of Na^+ or Ca^{2+}) in accordance with an embodiment of the present invention.

5 Fig. 24 shows release rates at pH 5 of theophylline from tablets obtained from maltodextroses grafted with acrylic acid (1:5) in accordance with an embodiment of the present invention.

Fig. 25 shows release rates at pH 7 of theophylline from tablets obtained from maltodextroses grafted with acrylic acid (1:5) in accordance with an embodiment of the present invention.

Fig. 26 shows the release rate at pH 5 of theophylline from tablets of potato starch grafted in the presence of organic solvents in accordance with an embodiment of the present invention.

Fig. 27 shows the release rate of theophylline from tablets of potato starch grafted in the presence of organic solvents with or without calcium ions in accordance with embodiments of the present invention.

Fig. 28 shows the effect of mono- and divalent cations on work of adhesion for grafted starches in accordance with the present invention.

Fig. 29 is a schematic diagram of the test apparatus for measuring bioadhesion.

20 Fig. 30 is a graph of force (Y-wxis) against extension (X-axis) for a sample to be tested for bioadhesion.

DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

The present invention will be described with reference to certain embodiments and to certain drawings but the present invention is not limited thereto but only by the claims. In particular the present invention will be described with reference to starches from different sources being grafted with acrylic monomers using two initiation methods: initiation by radioactive ^{60}Co and initiation by CAN, but the present invention is not limited thereto but only by the claims. For instance, the present invention is not limited to radioactive ^{60}Co irradiation but may include other methods of irradiation, e.g. electron beam irradiation, or irradiation with other nuclear particles or high energy radiation, e.g. ultra-violet radiation, X-ray radiation. Further, the present invention will be described

mainly with reference to rice or potato starch but the present invention is not limited thereto but includes any form of starch, e.g. from other sources such as wheat starch and those given above.

The present invention will mainly be described with reference to the controlled
5 release of one of two drugs, salicylic acid and theophylline, from a bioadhesive carrier whose adhesive component is provided by an acrylic grafted starch or starch hydrolysate copolymer but the present invention is not limited thereto but only by the claims.

The present invention will mainly be described with reference to a mucoadhesive but the present invention is not limited thereto. The present invention includes other
10 applications such as those applications where a bioadhesive is required which maintains its adhesive in wet conditions, for example, in the germination of seeds, the bioadhesive according to the present invention may be used to adhere active compounds such as herbicides, fertilisers or germination enhancers or other plant hormones to wetted seed or vegetable or plant tissue. The bioadhesive functionality may be used to advantage to allow
15 these compounds to remain in place even after initial or subsequent wetting in soil until the germination period is complete. The active ingredient in the bioadhesive may be a germination or growth hormone, an insecticide, fungicide, herbicide or any other pest control agent which is adhered to plants, crops or trees or foliage or roots thereof, or aquatic flora or fauna such as fish or other aquatic animals using the bioadhesive in
20 accordance with the present invention. The bioadhesive in accordance with the present invention may be used for controlled drug release to mucosal membranes of humans or animals such as membranes of the mouth, nose, lungs and bronchia, intestine, throat, vagina, rectum, eye or may be used for external use, e.g. for human or veterinary wound dressings, dressings for plants and trees or aquatic flora or fauna and particularly for
25 applications subject to influence, e.g. dislodging, by water based liquids such as urine or other body fluids including blood. For wound dressings the bioadhesive carrier in accordance with the present invention may be applied directly to an open wound and will bond thereto. Pharmaceutically active agents may be included in the bioadhesive carrier which may then be released in a controlled manner into the wound. The bioadhesive carrier
30 may also absorb exudate from the wound. The present invention also includes use in or on implantations in the human, animal or vegetable body. The uses of the present invention may include controlled drug release but this is not essential to the present invention, i.e.

the bioadhesive in accordance with the present invention also includes use for mechanical fixation purposes only or for the delivery of other active ingredients. For example, the bioadhesive in accordance with the present invention may be used in or on dental prostheses, e.g. in localisation and fixation of dentures or for the delivery of drugs or similar to specific regions of the mouth, e.g. the controlled delivery of local anaesthetics, antibiotics, antimyotics, antiseptics, antiviral drugs. The bioadhesive in accordance with the present invention may also be used in tablet form, e.g. with a soluble non-adhesive coating, for oral ingestion and subsequent internal delivery of an active compound or drug via the membranes of the oesophagus, stomach, colon or intestines.

The present invention will mainly be described with reference to inclusion of the bioadhesive agents in tablets but the present invention is not limited thereto. The bioadhesive agents in accordance with the present invention may be used in any suitable form, e.g. in beads or pellets, in microspheres or micro-or nano-capsules, in a mono-layer or in multi-layers, e.g. on a patch, or similar.

TEST METHODS AND MATERIALS

The following materials and test methods apply to all the embodiments of the present invention unless otherwise stated:

Materials

Starches from potato (S-4251), corn (S-4126) and rice (S-7260) were purchased from Sigma Chemical Co. Salicylic acid, acrylonitrile, polyacrylonitrile, acrylic acid and polyacrylic acid were bought from Aldrich Chemical Co. Acrylonitrile was freshly distilled before use. Theophylline was obtained from Ludeco, Belgium. Ceric ammonium nitrate (CAN) was Fisher Certified ACS grade or bought from Aldrich. Irradiation with ^{60}Co at an intensity of 1300 rad/min were performed at the Nuclear Engineering Department of Ben-Gurion University.

Intrinsic viscosity

The intrinsic viscosity of polyacrylonitrile was determined by measuring the viscosities of solutions at various dilutions with an Ubbelohde viscometer at 25°C.

Spectra

FT-IR spectra were registered with a Nicolet 410 FT-IR spectrometer. CP-MAS solid state ^{13}C -NMR spectra were obtained on a Bruker DMX-500 spectrometer.

5 Swelling

To determine the swelling property of a material an accurate weight of a small piece of graft copolymer was immersed in 200 ml of distilled water or various buffers and left to swell for 24 h or 48 h. The swollen piece was dried with filter paper and weighed. The ratio between swollen and dry weights was defined as the swelling extent.

10

Adhesive properties

To determine the bioadhesive characteristics of a material the following method was used. The apparatus used for the determination of the bioadhesive characteristics consisted of a tensile testing machine (type L1000R, Lloyd Instruments, Segenwordt, Fareham, UK), equipped with a 20 N load cell with an accuracy of less than 1%. The apparatus was connected to a computer. Porcine gingiva were obtained from a slaughter house directly after slaughtering. They were rapidly frozen and stored in isotonic phosphate-buffered saline pH 7.4 (2.38 g $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, 0.19 g KH_2PO_4 and 8.0 g NaCl made up to 1000 mL with demineralized water). Tablets of 100 mg of the material to be tested were directly compressed at a pressure of 1500 kg with the given polymers without any other excipient. An eccentric compression machine (Korsch, type EKO, Frankfurt, Germany) equipped with 7-mm flat punches was used. The test equipment for measuring bioadhesion is shown schematically in Fig. 29. The tablet 10 under test was attached to the upper aluminum support 14, connected to the superior cross-sectional bar 16 of the tensile tester with cyanoacrylate glue (Loctite Super Glue gel, Loctite Belgium, Kontich, Belgium). The porcine gingival tissue ($\pm 100 \text{ mm}^2$) 10 was glued (mucosal side out) with the same adhesive to a Teflon support 18, which was connected to a PVC cylinder 20 situated at the bottom of a 150 mL thermostatted beaker 22 fixed on the base on the tensile tester. Next, 15 μL of isotonic phosphate buffer (pH 7.4) was spread evenly over the mucosa 10, and the crosspiece 16 (bearing the tablet 12) was lowered at a crosshead speed of $1 \text{ mm} \cdot \text{min}^{-1}$. After initial contact, the thermostatted beaker 22 was filled with the buffer solution up to a total volume of 125 mL to act as a counterweight.

The mucosa 10 and the tablet 12 were then pressed together with a force of 0.5 N for 5 min, after which the tablet 12 and mucosa 10 were pulled apart at a constant extension rate of 5 mm.min⁻¹ until complete rupture of the tablet-mucosa bond was obtained. A force vs extension diagram (Fig. 30) was constructed, and the maximal detachment force and the work of adhesion necessary to break the bond between tablet and mucosa were calculated. The work of adhesion is calculated from the area under the force/extension diagram.

Acid Hydrolysis

To perform acid hydrolysis of grafted starch a suspension of 1 g of grafted copolymer in 20 ml of 1 N HCl was heated to boiling. After 2 h, the mixture was cooled to room temperature and centrifuged. To a sample from the supernatant, was added a solution of I₂/KI (see McCracken, D.A., Chain, I.R., Amylose in floridean starch. *New Phytol.*, 88, 1981, 67) to test for the presence or absence of starch. In parallel, the presence of sugar moieties in the supernatant was determined by the dinitrosalicylic acid method (see Bernfeld, P., *Methods Enzymol.* 1, 1955, 149).

FIRST EMBODIMENT: PREPARATION OF STARCHES GRAFTED WITH ACRYLONITRILE (1:1.5 W/W) BY CAN INITIATION

In accordance with a first embodiment of the present invention graft copolymers were prepared by chemical initiation. A stirred slurry of 10 g of starch in 167 ml of water was heated for 30 min at 85°C, while a stream of nitrogen was allowed to bubble slowly through the mixture. The mixture was then cooled to 25°C. Acrylonitrile (15.0 g, 0.283 mole) was added to the starch suspension, followed after about 1 min by a solution of ceric ammonium nitrate (0.338 g, 6.17 × 10⁻⁴ mole) in 3 ml of 1 N nitric acid. The reaction mixture was stirred under nitrogen for 2 h, and in most reactions sodium hydroxide solution was then added to give a pH of 7. Ethanol (200 ml) was added, and the crude graft copolymer was isolated by filtration, washed with ethanol, and dried *in vacuo* at 60°C. Selected crude graft copolymers were subjected to repeated extractions at room temperature with DMF to remove polyacrylonitrile homopolymer, and both the DMF solution and main product were analyzed by IR spectroscopy for the presence of -CN groups.

SAPONIFICATION OF PAN-CONTAINING GRAFTED STARCH

To characterise bioadhesive agents in accordance with the present saponified PAN-containing grafted starches were prepared. A suspension of 1 g of chemically initiated graft polymer in 20 ml of 0.5 N sodium hydroxide solution in a 125-ml

5 Erlenmeyer flask was heated on a steam bath until the mixture assumed a red-orange color and thickened sufficiently to preclude settling on standing (about 5-15 min of heating was required). The flask was loosely stoppered to permit the escape of ammonia, and was then placed in an oven at 95-100°C (for 2 h). The length of time in the oven required to cause the red-orange color to fade to a light yellow (an indication that saponification had gone to

10 completion) was noted. The reaction product was put in water and allowed to swell for about 68 h until constant absorbency values were obtained.

SECOND EMBODIMENT: PREPARATION OF STARCHES GRAFTED WITH ACRYLIC MONOMERS BY ⁶⁰Co IRRADIATION

15 In accordance with a second embodiment of the present invention, starches (2% or 5% w/v) were gelatinized and mixed with various amounts of acrylic acid. When graft copolymers were obtained by irradiation, acrylic acid was preferred as the monomer, since acrylonitrile is not soluble in the aqueous starch solution. However, acrylonitrile may also be used if the mixture with starch comprises an organic solvent. The mixtures were

20 exposed to ⁶⁰Co irradiation, usually for 24 h. The gels so formed were cut into small pieces and dried in air.

THIRD EMBODIMENT: THE USE OF MONO- AND DIVALENT CATIONS ON THE GRAFT COPOLYMERS

25 In accordance with a third embodiment of the present invention, the acrylic acid monomer was partially neutralized with mono-valent and/or divalent cations, e.g. sodium hydroxide, calcium oxide or magnesium oxide, and the pH of the mixture of acrylic acid and the acrylate salt formed was measured. Thereafter, grafting was performed as described above. The effect of the mono- and divalent cations was to introduce salts of the

30 acrylic side chains of the graft copolymer. In particular, the effect of the mono- and divalent cations on the behavior of graft copolymers with regard to swelling, release rates and bioadhesion were determined.

FIRST SERIES OF DRUG RELEASE STUDIES

To test the bioadhesive system according to the present invention two methods were used to load the model drugs salicylic acid and theophylline into the graft copolymers obtained by the methods of the first to third embodiments mentioned above. In the release studies, each value represents the mean \pm the standard deviation of three experiments.

FIRST METHOD OF INCORPORATION OF THE DRUG DURING SWELLING OF THE GRAFT COPOLYMER IN BUFFER SOLUTION

The kinetics of drug release were followed in a Hanson Research Corporation tablet dissolution system connected to a Spectronic 1201 spectrophotometer (Milton Roy) operated with Dissolution Software 10F1, version 1.01. A sample of weighed dry graft copolymer was added to saturated solution of the model drug (10 mg/ml for sodium salicylate, and 1 mg/ml for theophylline) in phosphate buffer 0.03-0.05 M, pH 7.4. The graft copolymer was left to swell for 24 h, after which time it was dried between two pieces of filter paper until no further changes in weight were measured. The weight of the incorporated drug was calculated as follows:

$$w_{\text{drug}} = \left(\frac{w_1 - w_0}{d} \right) \times c$$

20

where w_0 - weight of dry graft copolymer
 w_1 - weight of swollen graft copolymer
 d = density of solution (g/ml)
 c = concentration of drug (g/ml).

25

The swollen graft copolymer containing the drug was then immersed in phosphate buffer (900 ml), and the mixture was stirred at 65 rpm at 37-38°C. Samples were withdrawn every 30 min for 10 h; the absorbance was read on a UV-Vis spectrophotometer ($I_{\text{max}} = 297$ nm for sodium salicylate; $I_{\text{max}} = 272$ nm for theophylline); and the % of drug released was calculated.

30

Second method: Preparation of sustained-release tablets

In accordance with a second method the model drug was incorporated into tablets. In accordance with a one preparation procedure tablets were prepared with a binder as an excipient. Samples of graft copolymers were dried at room temperature, and then ground
5 in a blender cooled with liquid nitrogen. The powder was sieved through a 20-mesh sieve. The obtained material was mixed with the relevant model drug and polyvinylpyrrolidone as a binder in a ratio of graft copolymer:model drug:polyvinylpyrrolidone of 10:1:0.5. The solid mixture was wetted with ethanol and mixed further. The paste was dried in a thermostatically controlled oven at 50°C to a constant weight. The dry material was
10 ground, and then a mixture of syloid and magnesium stearate in a ratio of 2:1, which did not exceed 3-5% of the ground powder, was added. After proper mixing and sieving (20 mesh), tablets were pressed from the mixture in a cast, diameter $d = 8$ mm at a pressure of 2000-3000 psi. Each tablet weighed 0.25 ± 0.02 g and had a diameter of 9.0 ± 0.2 mm and a height of 4.0 ± 0.2 mm.

15 In a modification of the second method the same procedure was followed, except that no binder was used and after sieving, the drug was added to the graft copolymer at a ratio of 1:10.

Characterization of graft copolymers obtained by redox initiation with CAN in accordance with the first embodiment
20

In the case of Ce^{4+} redox initiation, in accordance with the first embodiment of the present invention, acrylonitrile (AN) may be used as monomer and grafting may be performed according to the method of Fanta et al. described in "Adsorbent polymers from starch and flour through graft polymerization of acrylonitrile and comonomer mixtures",
25 *Starch*, vol 30, 1978, 237-242, and shown schematically in Fig. 1. The results obtained for various weight ratios of starch to AN are presented in Table 1.

As can be seen from Table 1, the nitrogen content was somewhat higher for a weight ratio of starch to acrylonitrile of 1:5, but the polymerization of the monomer was lower (a large amount of acrylonitrile monomer was wasted without polymerization).
30 Homopolymer of polyacrylonitrile (PAN) formed as a by-product was washed out by extraction with DMF (dimethylformamide), and the presence of PAN grafted onto the starch was ascertained by FT-IR spectroscopy (Fig. 2).

Table 1. Grafting of starches with acrylonitrile (AN) by redox initiation¹

Starch source	Ratio of reagents (starch:AN)	Nitrogen in crude grafted starches ² (%)	Polymerization of AN monomer (%)
Potato	1:0.5	2.3	14.1
Rice	1:0.5	1.2	6.6
Potato	1:1	6.2	24.1
Rice	1:1	6.1	24.2
Potato	1:1.5	9.3	36.2
Rice	1:1.5	11.5	42.2
Potato	1:5	12.2	14.5
Rice	1:5	16.7	30.7

¹The redox system was based on CAN (ceric ammonium nitrate);²Total nitrogen content before extraction of homopolymer with DMF.

5

Table 2. Characterization of grafted starches with polyacrylonitrile (PAN)

Starch source	Ratio of reagents (starch:AN ¹)	Nitrogen after extraction with DMF (%)	PAN grafted onto starch (%) ²	Yield (%)	Add-on ³ of PAN (%)
Potato	1:1	4.6	82	50	17
Rice	1:1	5.4	89	41	26
Potato	1:1.5	8.8	95	67	36
Rice	1:1.5	10.2	89	61	37
Potato	1:5	11.9	98	27	43
Rice	1:5	15.7	94	41	57

¹ AN = acrylonitrile.²The percentage was calculated from the ratio of nitrogen content in the grafted starch and total nitrogen at the end of reaction.10 ³Add-on was defined as weight percent of PAN in the grafted starch.

From nitrogen analysis (Table 2), the extent of homopolymerization was estimated, as

could the percent of PAN grafted onto the starch. The yields of the starches grafted with PAN varied, the best yield being obtained for materials in which the ratio of starch to acrylonitrile was 1:1.5.

5 Basic hydrolysis of grafted copolymers

Further characterization of the starches grafted with PAN was continued mainly with materials in which the weight ratio of starch to acrylonitrile was 1:1.5 or 1:5, as shown in Table 2. After extraction of the homopolymer with DMF, the remaining grafted copolymer was hydrolyzed in alkali (according to the lower scheme of Fig. 1, results are given in Table 3). In the FT-IR spectrum, the peak of the -CN group disappeared, while that of the carboxylic groups appeared at 1737 cm^{-1} . The presence and extent of some amide groups in the copolymer was confirmed by nitrogen analysis (Table 3) and by FT-IR (Fig. 3).

15 Table 3. Efficiency of basic hydrolysis of grafted starches with polyacrylonitrile (PAN)

Starch source	Ratio of reagents (starch:AN)	Nitrogen after basic hydrolysis (%)	Conversion of PAN in grafted starches to PAA (%)
Potato	1:1	0.9	80
	1:1.5	1.7	79
	1:5	0.8	93
Rice	1:1	1.2	79
	1:1.5	2.6	75
	1:5	0.7	96

AN = acrylonitrile, PAA = polyacrylic acid.

Acid hydrolysis of starch-g-polyacrylonitrile

From the point of view of further structural determination, the characterization of the grafted copolymers regarding points of attachment of polyacrylic moieties to starch and the molecular weight of the polyacrylic chains was investigated. Since the grafted copolymers obtained by either method (chemical initiation or irradiation) were insoluble in water, conventional methods for molecular weight determination could not be used. Accordingly, the starch-g-polyacrylonitrile backbone was degraded by acid hydrolysis

(HCl, 1 N) and molecular weights of the resulting polyacrylonitrile and/or polyacrylic acid chains determined (the scheme of Fig. 4). At the end of the hydrolysis stage, the absence of starch was proved by testing the solution with I₂/KI (see McCracken, D.A., Chain, I.R., Amylose in floridean starch. *New Phytol.*, **88**, 1981, 67). In parallel, the presence of sugar
 5 moieties was determined by the dinitrosalicylic acid method (see Bernfeld, P., *Methods Enzymol.* **1**, 1955, 149).

Table 4. Acid hydrolysis of grafted starches with acrylonitrile (AN)

Starch source	Ratio of reagents (starch:AN)	Nitrogen after hydrolysis (%) ¹	Decrease in weight after hydrolysis (%)
Potato	1:1.5	24.0	28
Rice	1:5	24.0	53

¹Theoretical nitrogen percentage in polyacrylonitrile 27.8%.

10

Table 5. Number-average molecular weight (M_n) of polyacrylonitrile (PAN) residues calculated from measurements of intrinsic viscosity

Starch source	Ratio of reagents (starch:AN)	Intrinsic viscosity of PAN (dl/g)	M _n of PAN	Attachment frequency of PAN ¹
Potato	1:1.5	3.37	150,000	1200
Rice	1:5	5.4	330,000	1500

Intrinsic viscosity was measured with a Ubbelohde capillary viscometer.

¹Attachment frequency reflects the number of glucose units between PAN chains.

15

The PAN obtained from the acid hydrolysis of the chemically grafted potato or rice starches was soluble in DMF (Table 4). The molecular weight (M_n) of the PAN residues was calculated using the relationship between the intrinsic viscosity and the molecular weight (equation 1). The constants in eq. 1 were obtained from studies on molecular
 20 weight determination of polyacrylonitrile (see Onyon, P.F., *J. Polym. Sci.* **XXII**, 1956, 19-23, or Cleland, R.L., Stockmayer, W.H., *J. Polym. Sci.* **XVII**, 1955, 473-477):

$$[\eta]_{DMF}^{25^\circ} = 3.92 \times 10^{-4} M_n^{0.75} \quad (1)$$

The intrinsic viscosity was determined by measuring the viscosity of diluted solutions of PAN in DMF. The results are presented in Table 5.

5 Swelling of grafted copolymers obtained by redox initiation

The extent of swelling of the chemically prepared grafted starches with PAN in accordance with the first embodiment is an important parameter since the extent of swelling strongly influences the bioadhesive properties. The extent of swelling was tested in water at pH 2, 5 and 7 and in citrate, acetate and phosphate buffers, having different pH
10 values. The results presented in Fig. 5 describe the swelling behavior of a sample of rice starch grafted with polyacrylic acid (weight ratio 1:1.5 rice starch to acrylonitrile). Both in water and in citrate buffer at low pH, the swelling was low, probably due to the presence of non-ionized -COOH groups. With an increase in pH to pH 4.5-5.0, the swelling increased due to ionization of the carboxylic groups. Between pH 5-8 the swelling leveled
15 off.

Effect of irradiation time on release of model drugs from grafted starches

The effect of irradiation time on the release of salicylic acid and theophylline from grafted starches in accordance with the second and third embodiments is shown in Fig. 6
20 and Fig. 7, respectively. Grafting by ^{60}Co irradiation was performed for various periods of time. After stopping the irradiation, drugs were incorporated in the starch-grafted copolymers, and the kinetics of drug release were followed. Although it is clear from Fig. 6 and Fig. 7 that longer irradiation times increased the time required to release the loaded drug, the behavior of each model drug is better understood from the correlation of the rate
25 of drug release with irradiation time, as presented in Fig. 8. The release rate of salicylic acid, the smaller of the two molecules, was retarded only after long periods of irradiation (more than 8 h), whereas the release of theophylline was at least approximately indirectly proportional to irradiation time. To test the reproducibility of the findings, further experiments were run for 24 h (see below).

30

Effect of weight ratio of starch to acrylic acid

Grafting of starch (2 wt.%) solutions with various amounts of acrylic acid was

carried out using two types of starch (potato starch and rice starch) grafted with acrylic acid by the irradiation method of the second embodiment. Grafting of potato starch was performed with various amounts of acrylic acid (0.2, 0.5, and 1.0 g). The release of salicylic acid as a function of time is presented in Fig. 9 which also shows the weight ratios of potato starch to acrylic acid. When acrylic acid was grafted onto rice starch, similar or even higher amounts of acrylic acid were used (Fig. 10). For the potato starch-g-acrylic acid copolymers obtained with < 1 g of acrylic acid (weight ratio 1:1), the release was relatively fast (about 1 h). When the amount of acrylic acid was increased, the release of salicylic acid was retarded, less than 80% being released after about 5 h (Fig. 7, ■). When rice starch was grafted, even with low amounts of acrylic acid, the release of salicylic acid was slow (about 80% in 6 h) (Fig. 8, ●).

Grafting of starch solution (5 wt %) with small amounts of acrylic acid was also carried out. For instance, potato starch in a higher concentration (5 wt.%) was also grafted with small amounts of acrylic acid by the irradiation method (Fig. 11). Again, when a small amount of acrylic acid was added, the release of salicylic acid was relatively quick (about 2 h). When the amount of acrylic acid was doubled, the release curve was similar to that in Fig. 9, where less starch was used but the ratio was kept the same.

A comparison of the release curves of salicylic acid from potato starch-g-acrylic acid copolymer obtained with 2 or 5 wt % starch and the same amount of acrylic acid is presented in Fig. 12. The difference in the release curves is not significant although the release is quicker with higher amounts of starch.

The slow release of theophylline from starch-g-acrylic acid copolymers obtained from 2 wt.% starch and higher amounts of acrylic acid was also investigated (Fig. 13). The release of theophylline was significantly delayed as the amount of acrylic acid in the graft copolymer was increased. When the ratio of starch to acrylic acid was 1:12.5, total release of the model drug was obtained in about 10 h. However, when the ratio was tripled by increasing the amount of acrylic acid, only about 60% of the drug was released in the same period of time.

In accordance with an embodiment of the present invention, the incorporation of the active component, e.g. salicylic acid or theophylline, was performed by allowing dry grafted starches in accordance with the present invention to swell during the incorporation of the respective model drug. A comparative experiment was performed with a sample of

dry grafted starch and a tablet obtained from the powdered form of the same grafted copolymer. Powders obtained after milling under liquid nitrogen were used to prepare tablets with the model drugs as described above. Tablets with binder (polyvinylpyrrolidone) were also prepared. The results in Fig. 14 show better release of the drugs from the
5 tablets.

The release of theophylline from tablets obtained with graft copolymers from both potato and rice starch in accordance with the present invention with the same amount of theophylline is presented in Fig. 15. The release of the drug was significantly slower from the rice starch-g-acrylic acid copolymer (only about 70% release after 8 h). When binder
10 was added to tablets prepared from the same batches of graft copolymers, the release of theophylline (Fig. 16) was similar for both rice and potato starch grafted copolymers. According to these results the binder may be used advantageously in accordance with the present invention to eclipse the differences observed above and shown in Fig. 15.

Acid hydrolysis of grafted copolymers obtained by irradiation in accordance with
15 the second and third embodiments was performed in order to free the polyacrylic acid chains for molecular weight determination. However, the remaining polyacrylic acid was found to be insoluble in water. In order to avoid what seems to be crosslinking of polyacrylic acid during irradiation, acrylic acid partially neutralized with NaOH, CaO and MgO was mixed with the respective starch prior to the grafting process. Thus, acrylic acid
20 neutralized with increasing amounts of base was grafted onto potato starch. After grafting, drying and milling, samples of these copolymers were subjected to acid hydrolysis. The same behavior was obtained: the polyacrylate chains formed weak gels in water. It seems that during the grafting process, some cross-linking of the polyacrylic acid in the graft occurs, which affects the solubility of the polyacrylic acid chains in aqueous solutions over
25 a wide range of pH values (pH 1-8).

The effect of partly neutralising and partial ionisation of the acrylic moiety of the grafted starch copolymer was determined. In particular, mono- and divalent cations were included in the grafted starches in accordance with the third embodiment and their effect on the release rate of theophylline from tablets and on the extent of bioadhesion
30 determined. In particular, the effects of different cations, of the pH of the dissolution medium and of the type of starch on release kinetics of theophylline from tablets were determined.

The kinetics of theophylline release from the corn starch polymer as a function of time (Fig. 17) were similar in the presence or absence of sodium ions. However, the release of the drug was modified by incorporation of the divalent cations tested, Mg^{2+} and Ca^{2+} . In the case of calcium ions, only about 55% of theophylline was released after about 10 h, while in the presence or absence of Na^+ , 90% of the drug was released in about 6 h. The release rate of theophylline was similar irrespective of the type of starch used in the graft polymerization (Fig. 18 and 19). When higher amounts of cations ($\times 2$, $\times 4$) were added to acrylic acid before grafting, the release of theophylline was faster in the presence of calcium ions than in the presence of sodium or magnesium cations.

When the rate of theophylline release was tested in dissolution medium at various pH values (pH 3, 5 and 7), it was found that the release rate did not depend on the pH (Fig. 17-19).

Similar behavior regarding effect of ions and pH of dissolution medium was observed with other embodiments of the present invention which use maltodextroses (#1924 and #1910, respectively) grafted with acrylic acid (Fig. 20 and 21) rather than starches.

EFFECT OF INCREASING DRUG LOADING ON THE DRUG RELEASE RATE OF FROM TABLETS

In the above experiments about 10% of the model drug was loaded into the tablets prepared with the grafted starches in accordance with the present invention. The time required to release about 80% of the drug depended on the type of starch, the method of initiation of the grafting, the type of model drug chosen, the presence or absence of binder during tablet preparation, and the presence of mono- or divalent cations in the graft copolymer. The kinetics of drug release showed that 2-10 h were required for the release of 50 to 80% of the drug.

When the effect of the amount of drug—salicylic acid or theophylline—loaded into the tablet was tested, it was found that, in a dissolution medium at pH 5, the fastest release rate was obtained from a tablet comprising 50% salicylic acid and 50% rice starch acrylic acid graft copolymer starch to acrylic: 1:5 prepared in the presence of calcium ions in accordance with the third embodiment (Fig. 22). The rate of theophylline release (only 10% loading) was slower than for salicylic acid (20 or 50% loading).

The influence of increasing amounts of theophylline on the release of the drug from tablets in a dissolution system at pH 5 is illustrated in Fig. 23. The tablets were prepared from corn starch grafted with acrylic acid partially neutralized with NaOH or CaO in accordance with the third embodiment. In copolymers prepared with Na⁺, the same kinetics of drug release were observed for 10% and 20% theophylline. However, increasing the theophylline content to 50%, slowed down the release rate of the drug. When tablets were prepared from grafted corn starch that contained calcium ions (third embodiment), the release rate of theophylline (10 and 20%) slowed dramatically (about 50% after 10 h). Thus, the presence of calcium - rather than the degree of loading - became the factor determining the release rate of the drug.

EFFECT OF MALTODEXTROSE OLIGOMER SIZE ON THE RELEASE OF THEOPHYLLINE FROM GRAFTED MALTODEXTROSE

In accordance with a fourth and a fifth embodiment of the present invention a series of maltodextroses of various oligomer sizes. i.e., various degrees of dextrose equivalency (DE) were grafted with acrylic acid (ratio 1:5) in the presence (fourth embodiment) or absence (fifth embodiment) of calcium ions. The release of theophylline from tablets prepared with the grafted maltodextroses was tested in two dissolution media, i.e., pH 7 and pH 5. Results presented in Fig. 24 and Fig. 25 show a correlation between the size of the maltodextrose oligomer (DE) and the release rate of theophylline. Here again, the significant effect of calcium ions is expressed in the lowering of the release rate of the drug. The sample 19-39-10, which contained calcium ions, was prepared from maltodextrose #1906, with a DE of 6. The release rate from the non-calcium-containing analog, maltodextrose #1906 (19-39-2), was very rapid (Figs. 24 and 25).

EFFECT OF SOLVENT ADDED DURING THE GRAFTING PROCESS ON THE RELEASE RATE OF THEOPHYLLINE FROM TABLETS

The usual procedure for grafting acrylic acid into starches was performed in water. In accordance with a sixth embodiment of the present invention, the acrylic moiety, e.g. acrylic acid was dissolved in organic solvents such as ethanol and acetone was added to the pregelatinized starch in water, and the mixture was then subjected to ⁶⁰Co radiation in accordance with the third embodiment. In a seventh embodiment of the present invention,

partially neutralized acrylic acid in the form of calcium acrylate was used.

The results presented in Fig. 26 describe the release of theophylline from tablets prepared from copolymers grafted in acetone:water (1:9), acetone:water (1:5) and ethanol:water (3:7). In Fig. 27 the drug release obtained with potato starch grafted in either ethanol:water (1:9) or acetone:water (1:9) with or without calcium ions is presented. The results show that longer periods of time were required to release theophylline from tablets prepared with starch grafted in a mixture of water and organic solvent. However, under these conditions, the higher the content of organic solvent, the more rapid the release of drug from the tablets. In contrast to starches grafted in aqueous media, the presence of calcium in the organic solvents did not have any effect on the release rates of theophylline.

MECHANISM OF DRUG RELEASE

The amount of theophylline released from tablets (%) was correlated to the release time by equation (2):

$$M_t/M_i = kt^n \quad (2)$$

where M_t/M_i is the amount of drug (%) released at time t (min), n is a diffusional exponent and k is the apparent release rate (Table 6).

The release behavior of graft copolymers was found to be non-Fickian (in all cases the n value was between 0.6 and 1.1). This points to a mechanism of release which is a combination of the diffusion of theophylline from the matrix and the swelling of tablet after water penetration into the tablet. This combined effect may be used to advantage in accordance with the present invention to provided controlled and/or sustained release of an active component such as a drug.

Table 6. Kinetic release constants (k) and release exponent (n) of the release of theophylline from tablets of graft copolymers

Sample	pH 3		pH 5		pH 7		Remarks
	k	n	k	n	k	n	
18-18-1 p. starch	0.64	0.871					Without ions
18-64-1 p. starch	0.27	1.03					Na ⁺
18-64-2 p. starch	1.04	0.671					Ca ⁺⁺
18-64-3 p. starch	1.46	0.64					Mg ⁺⁺
18-53-8 mixed batches p. starch	1.45	0.817	1.20	0.843	2.69	0.989	Without ions
18-106-1 r. starch	0.65	0.918	0.45	0.973	0.44	0.964	Na ⁺
18-106-2 r. starch	1.48	0.608	0.96	0.649	0.63	0.767	Ca ²⁺
18-106-3 r. starch	1.31	0.635	0.87	0.691	0.65	0.777	Mg ²⁺
18-106-11 c. starch	0.55	0.932	0.53	0.936	0.45	0.948	Na ⁺
18-106-12 c. starch	1.52	0.59	1.11	0.62	0.65	0.757	Ca ²⁺
18-106-13 c. starch	1.38	0.640	0.92	0.702	0.69	0.788	Mg ²⁺
19-11-1 r. starch					0.53	0.786	no AA
18-106-4 #1910	0.49	0.881			0.37	0.994	Na ⁺
18-106-5 #1910	1.19	0.649			0.56	0.740	Ca ²⁺
18-106-6 #1910	1.32	0.649			0.421	0.856	Mg ²⁺
18-106-7 #1924	-	-	0.57	0.814	0.49	0.871	Na ⁺
18-106-8 #1924	1.52	0.600	1.28	0.541	1.10	0.579	Ca ²⁺
18-106-9 #1924	1.56	0.616	1.503	0.59	1.29	0.622	Mg ²⁺

AA = acrylic acid.

5 SWELLING OF GRAFTED COPOLYMERS IN WHICH THE ACRYLIC ACID MONOMER WAS PARTIALLY NEUTRALIZED WITH MONO- AND DIVALENT CATIONS

In the design of a bioadhesive, e.g. a buccal bioadhesive, one of the important characteristics can be the extent of swelling. It is desirable for the preparation to have moderate swelling: low swelling will prevent adhesion, while a high degree of swelling will

result in "slippery" materials, which may not adhere satisfactorily to the mucus membrane.

The extent of swelling was measured not only to test reproducibility but also to define homogeneity of graft copolymers obtained by scaling-up the grafting reaction by ^{60}Co initiation. Gels were cut into slices, and from each slice, samples were cut out and air dried. Representative results are shown in Table 7. It can be seen that the swelling ratio was in the range of 20 to 60 times after 48 hours whereby the swelling ratio after 24 hours was about 50% of the swelling after 48 hours.

Table 7. Swelling of pieces from slices of potato starch grafted with acrylic acid

Sample ¹	Initial weight (mg)	Weight after 24 h (g)	Swelling ratio	Weight after 48 h (g)	Swelling ratio
18-53-1	46.1	1.3	28.2	2.7	58.5
18-53-2	45.0	0.7	15.5	1.1	24.4
18-53-3	45.9	1.6	34.8	2.4	52.3
18-53-4	45.3	2.2	48.7	2.7	59.6
18-53-5	45.2	1.3	28.8	2.3	50.9
18-53-6	44.1	1.4	31.7	2.3	52.1

¹The last number in the sample designation represents the slice from a large-scale preparation of graft copolymer of potato starch and acrylic acid (weight ratio 1:5) obtained with ^{60}Co initiation.

Since the effect of partial neutralization of the acrylic acid moiety before grafting in accordance with the third embodiment of the present invention was found to influence the final properties of graft copolymers in terms of theophylline release, the extent of swelling of these copolymers was also measured. The swelling ratio were higher than those of table 7 by up to a factor of about ten. In comparison with sodium, incorporation of calcium and magnesium into the grafts resulted in the extent of swelling decreasing dramatically. An even more pronounced decrease in swelling was observed when the amount of the divalent cations added before grafting was increased (Table 8).

Table 8. Swelling of graft copolymers obtained with partially neutralized acrylic acid

Sample	Initial weight (mg)	Weight after 24 h (g)	Swelling ratio	Description
18-106-1	46.7	22.3	477.5	r. starch:AA + Na ⁺ (× 1)
18-106-2	53.2	5.5	103.4	r. starch:AA + Ca ²⁺ (x1)
18-106-3	47.6	7.0	147.0	r. starch:AA+ Mg ²⁺ (× 1)
18-106-11	49.8	30.9	620.5	c. starch:AA + Na ⁺ (× 1)
18-106-12	54.2	9.1	167.9	c. starch:AA + Ca ²⁺ (× 1)
18-106-13	52.5	7.6	144.8	c. starch:AA + Mg ²⁺ (× 1)
18-99-1	52.1	31.3	591	p. starch:AA + Na ⁺ (x2)
18-99-2	39.6	0.08	2.1	p. starch:AA + Ca ²⁺ (× 2)
18-99-3	44.3	0.08	1.7	p. starch:AA + Ca ²⁺ (× 4), pH 5.5
18-99-5	55.3	5.9	106.2	p. starch:AA + Mg ²⁺ (× 2), pH 3.3
18-99-4	53.9	0.10	1.9	p. starch:AA+ Mg ²⁺ (× 4), pH 8.1

r = rice, c = corn, p = potato, AA = acrylic acid.

5 Table 9. Swelling of graft copolymers obtained from maltodextroses with partially neutralized acrylic acid

Sample	Initial weight (mg)	Weight after 24 h (g)	Swelling extent	Description
18-106-4	49.4	44.7	918.8	#1910:AA + Na ⁺
18-106-5	51.5	10.8	209.7	#1910:AA + Ca ²⁺
18-106-6	50.4	20.3	402.8	#1910:AA + Mg ²⁺
18-106-7	51.4	86.9	1690	#1924:AA + Na ⁺ (× 1)
18-106-8	51.2	50.1	978.5	#1924:AA + Ca ²⁺
18-106-9	52.3	61.2	1170	#1924:AA + Mg ²⁺

AA = acrylic acid, PAA = polyacrylic acid.

The extent of swelling of grafted maltodextroses with partially neutralized acrylic acid is presented in Table 9. Although very high swelling was obtained with both maltodextroses in the presence of mono- and divalent cations, the presence of calcium lowered the swelling significantly, especially in the case of maltodextrose #1910.

5 In conclusion, it is evident that the extent of swelling as well as the release rate of theophylline from this type of graft copolymer can be modified and controlled by addition of divalent ions.

BIOADHESION MEASUREMENTS

10 Representative samples of grafted starches obtained by the two initiation methods (chemical or irradiation) were tested for their bioadhesive properties (Tables 10 and 11). The best bioadhesion was found for rice starch grafted with acrylic acid by the ^{60}Co irradiation method. Bioadhesion measured for starches grafted by the redox method were somewhat lower. One possible reason for this finding could be that the acrylic side chains
15 were probably cross-linked by the irradiation procedure. Another reason could be the fact that the final grafted starch obtained by the redox method had amide groups in addition to carboxylic groups (the scheme of Fig. 1). Since the results concerning nitrogen content in grafted starches after basic hydrolysis showed a low percentage of nitrogen left (Table 3), only a few amide groups were present in the graft copolymer. Another factor that proved
20 to be important was the pH of the final graft copolymer. At high pH, bioadhesion was low, due to the high density of anionic materials.

Table 10. Bioadhesion of grafted starches obtained by the two initiation methods

Sample #	Type of starch	Detachment force (N)	Work of adhesion (mJ)	Grafting method
JP-42-1	Potato	2.821 ± 0.758	0.864 ± 0.299	Irradiation
JP-42-2	Potato	1.271 ± 0.422	0.092 ± 0.057	Redox
JP-42-3	Rice	3.159 ± 0.785	0.872 ± 0.182	Irradiation
JP-42-4	Rice	1.372 ± 1.275	0.270 ± 0.323	Redox
Reference ¹		2.322 ± 1.298	0.443 ± 0.207	-

¹Physical mixture

EFFECT OF PH ON BIOADHESION

The effect of pH had to be tested in greater depth, not only on the preparations obtained by chemical initiation but also on materials prepared by irradiation. Some results are presented in Fig. 28.

5

Effect of mono- and divalent cations on bioadhesion

The extent of bioadhesion due to the presence of mono- and divalent cations in the graft copolymers is presented in Fig. 28 and in Table 11. The materials tested could be divided into three categories (Fig. 28):

- 10 1. Grafted rice starch prepared by chemical initiation with the $\text{Ce}^{3+}/\text{Ce}^{4+}$ redox system;
2. Starches (potato, corn, rice) grafted with acrylic acid partially neutralized with Na^+ , Ca^{2+} or Mg^{2+} , prepared by radiation with ^{60}Co ;
3. Copolymers of maltodextroses (#1910, #1924) grafted with acrylic acid in the
15 presence of mono- and divalent cations.

Results:

1. Grafted rice starch: At high pH (pH 10) at a ratio of starch to acrylic acid of 1:1.5, as expected, no bioadhesion was detected. After lowering the pH (pH 3), the same material showed some degree of bioadhesion. When the amount of acrylic acid was increased to a
20 ratio of starch: acrylic acid of 1:5, some bioadhesion was measured, even at pH 10.
2. Starches grafted with acrylic acid in the presence of mono- and divalent ions: In the presence of Na^+ , the extent of bioadhesion was similar for the three starches tested. When divalent cations (Ca^{2+} , Mg^{2+}) were introduced, the bioadhesion measured was always higher for materials containing Ca^{2+} than for those with Mg^{2+} . However, when Ca^{2+} and
25 Mg^{2+} were added in higher amounts ($\times 2$) and ($\times 4$), the degree of bioadhesion dropped completely.
3. Grafted copolymers of maltodextroses and acrylic acid: Two maltodextroses (#1910 and #1924) grafted with acrylic acid in presence of Na^+ , Ca^{2+} and Mg^{2+} behaved similarly to the various starches. Grafted starches containing Ca^{2+} were more adhesive than those
30 containing Na^+ or Mg^{2+} . In the case of the grafted maltodextroses, the materials containing Mg^{2+} showed higher bioadhesion. The difference between these two

maltodextroses lies in their degree of oligomerization, the larger oligomer being #1924, hence, the size of the oligomer seems to influence bioadhesion and possibly also drug release.

5 Table 11. Bioadhesion results

Sample	Ratio of reagents	Detachment force (N)		Work of adhesion (mJ)	
		mean	SD	mean	SD
J-5-10	r.st:AN = 1:1.5, pH5	3.178	0.536	0.553	0.156
J-5-1A	r.st:AN = 1:1.5 (5:1.5)	0.018	0.021	0.016	0.022
J-47-8	p.st:AN = 1:1.5 (6:1.5)	1.837	0.836	0.207	0.111
J-42-2	p.st:AN = 1:1.5, pH5	2.369	0.503	0.446	0.310
J-48-1	p.st:AN = 1:1.5 (2.5:1.5)	0.396	0.395	0.023	0.018
18-8-1	p.st:AA = :5	4.481	0.077	1.398	0.325
18-18-1	p.st:AA = 1:5	4.851	1.459	1.700	0.297
18-24-1	p.st:AA = 1:5	3.894	0.706	1.173	0.170
18-33-11	p.st:AA = 1:5 (batches)	2.899	0.223	0.842	0.101
18-43-7	p.st:AA = 1:5 (batches)	3.777	0.462	1.187	0.190
18-43-8	r.st:AA = 1:5	0.372	0.524	0.503	0.059
J-61-2	p.st:AA = 1:12.5	2.223	0.393	0.576	0.124
J-61-3	p.st:AA = 1:12.5	3.932	0.620	0.978	0.285
J-61-5	p.st:AA = 1:25	2.604	0.513	0.579	0.049
J-61-4	p.st:AA = 1:37.5	2.235	0.424	0.469	0.130
18-64-1	p.st:AA = 1:5+Na ⁺ (AA:Na = 0.27:0.05 mole)	3.262	0.498	0.896	0.214
18-64-2	p.st:AA = 1:5+Ca ²⁺ (AA:Ca = 0.27:0.04mole),pH 3.8	4.663	1.320	1.516	0.376
18-64-3	p.st:AA = 1:5+Mg ²⁺ (AA:Mg = 0.27:0.05 mole)	3.225	0.913	0.976	0.299
Ref.		2.812	0.488	0.450	0.143

Graft copolymers in accordance with the present invention achieve a work of adhesion greater than 0.1 mJ (6×10^{-3} mJ/mm²), and preferably a work of adhesion greater than 0.3 mJ (18×10^{-3} mJ/mm²). Some embodiments of the present invention achieved a work of adhesion greater than 1mJ (6×10^{-2} mJ/mm²).

5

IN-VIVO EXPERIMENTS IN DOGS

Tablets prepared from some grafted copolymers (Table 12) in accordance with the present invention were attached to the inside of the mouths of dogs (gingiva). The purpose of the experiments was to test whether toxicity and/or irritation developed with time. Data on the bioadhesion time of the tablets in the dogs' mouths is presented in Table 12. No irritation or toxicity was detected, even after the long periods of time.

Table 12. Adhesion times of tablets in dogs

Sample #	Sample characterization	Adhesion time (h)
18-106-1	Starch rice/AA 1:5 Na ⁺ (× 1)	12-24
18-106-2	Starch rice/AA 1:5 Ca ²⁺ (× 1)	>24
18-106-3	Starch rice/AA 1:5 Mg ²⁺ (× 1)	40
18-106-4	Malt.1910 1:5 Na ⁺ (× 1)	10-12
18-106-5	Malt.1910 1:5 Ca ²⁺ (× 1)	>24
18-106-6	Malt.1910 1:5 Mg ²⁺ (× 1)	>24
18-106-7	Malt.1924 1:5 Na ⁺ (× 1)	46
18-106-8	Malt.1924 1:5 Ca ²⁺ (× 1)	40
18-106-9	Malt.1924 1:5 Mg ²⁺ (× 1)	40
18-106-11	Starch corn/AA 1:5 Na ⁺ (× 1)	24
18-106-12	Starch corn/AA 1:5 Ca ²⁺ (× 1)	36
18-106-13	Starch corn/AA 1:5 Mg ²⁺ (× 1)	30
18-99-2	Starch potato/AA 1:5	12-24
19-22	Starch potato/AA 1:5 Ca ²⁺ (× 1)	12-24

CLAIMS

1. A bioadhesive agent wherein the bioadhesive property of the agent is provided substantially or mainly by a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative.
5
2. A bioadhesive system comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative.
10
3. An adhesive material for animal or human mucosa, skin, body tissue or vegetable or plant tissue, the material including a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative
15
4. Use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative in the manufacture of a bioadhesive agent.
- 20 5. A controlled release active component delivery vehicle comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of an acrylic-poly- α -glucoside graft copolymer.
6. Use of a graft copolymer of a poly- α -glucoside and at least a graft copolymerizable α , β -ethylenically unsaturated monocarboxylic acid or acid derivative as a bioadhesive agent in the
25 manufacture of a controlled release active component delivery vehicle.
7. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of the above claims, wherein the a graft is a poly- α 1,4 -glucoside graft copolymer or a poly- α -1,6
30 glucoside graft copolymer.
8. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of the

above claims, wherein the graft copolymer is a graft copolymer with a starch or a hydrolysate of a starch.

9. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of the
5 above claims, wherein the acrylic-poly- α -glucoside graft copolymer includes a graft copolymer of a poly- α -glucoside and at least one of acrylic acid and acrylonitrile.

10. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of
10 the above claims, wherein the graft copolymer is at least partly saponified.

11. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of
the above claims, wherein the graft copolymer includes a further grafted monomer selected
from an ester of acrylic acid and derivatives thereof, and an ester of methacrylic acid and
derivatives thereof.

12. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of
15 the above claims, wherein an active component is incorporated into the graft copolymer.

13. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of
20 the above claims, wherein an excipient is incorporated into the graft copolymer.

14. A bioadhesive agent, a bioadhesive system, a material or a vehicle according to any of
the above claims, wherein the bioadhesive agent has a work of adhesion of at least 6×10^{-3}
 mJ/mm^2 , more preferably a work of adhesion of at least $18 \times 10^{-3} \text{ mJ/mm}^2$.

25 15. Method of preparing a bioadhesive agent comprising the steps of:
grafting a poly- α -glucoside with at least a graft copolymerizable α , β -ethylenically
unsaturated monocarboxylic acid or acid derivative.

30 16. Method of preparing a bioadhesive agent comprising the steps of:
at least partially neutralising a graft copolymerizable α , β -ethylenically unsaturated
monocarboxylic acid, and

grafting a poly- α -glucoside with the at least partially neutralized acid.

17. The method of claim 16, wherein the neutralising step includes forming a monovalent or divalent salt.
- 5 18. The method according to any of the claims 15 to 17, wherein the grafting step includes a further grafted monomer selected from an ester of acrylic acid and derivatives thereof, and an ester of methacrylic acid and derivatives thereof.
- 10 19. The method according to any of claims 15 to 18, wherein an active component is incorporated into the graft copolymer.
20. The method according to any of the claims 15 to 19, wherein an excipient such as a binder is incorporated into the graft copolymer.
- 15 21. The method according to any of the claims 15 to 20, wherein the grafting step includes irradiation with a high energy source.
22. The method according to any of the claims 15 to 21, wherein the grafting step is carried
- 20 out in an aqueous or in an organic solvent.
23. A bioadhesive agent wherein the bioadhesive property of the agent is provided substantially or mainly by a copolymer of a poly- α -glucoside and at least an α , β -ethylenically unsaturated monocarboxlic acid or acid derivative.
- 25 24. A bioadhesive system comprising a bioadhesive agent, the bioadhesive agent comprising or consisting essentially of a copolymer of a poly- α -glucoside and at least an α , β -ethylenically unsaturated monocarboxlic acid or acid derivative.
- 30 25. Method of preparing a bioadhesive agent comprising the steps of:
copolymerising a poly- α -glucoside with at least an α , β -ethylenically unsaturated monocarboxlic acid or acid derivative.

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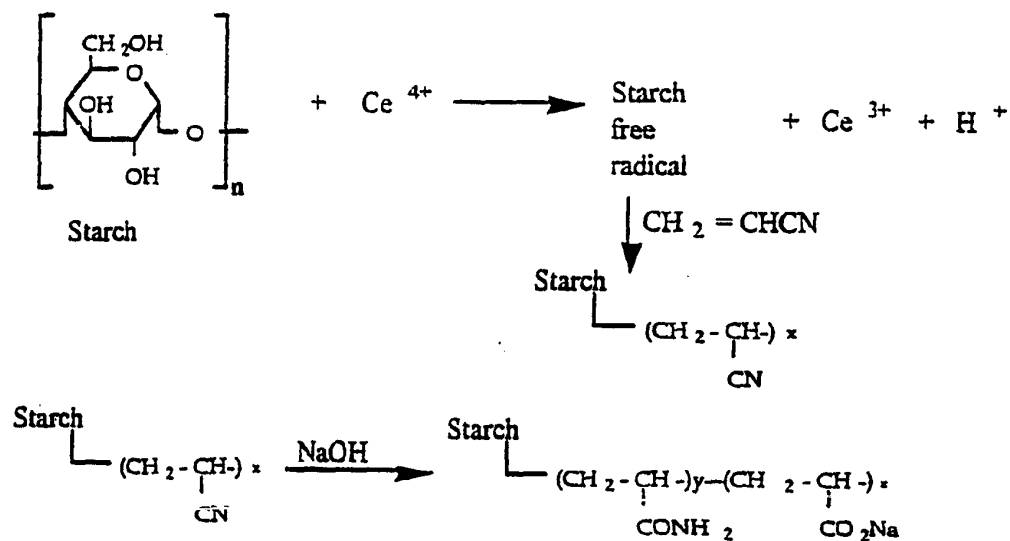


Fig. 1

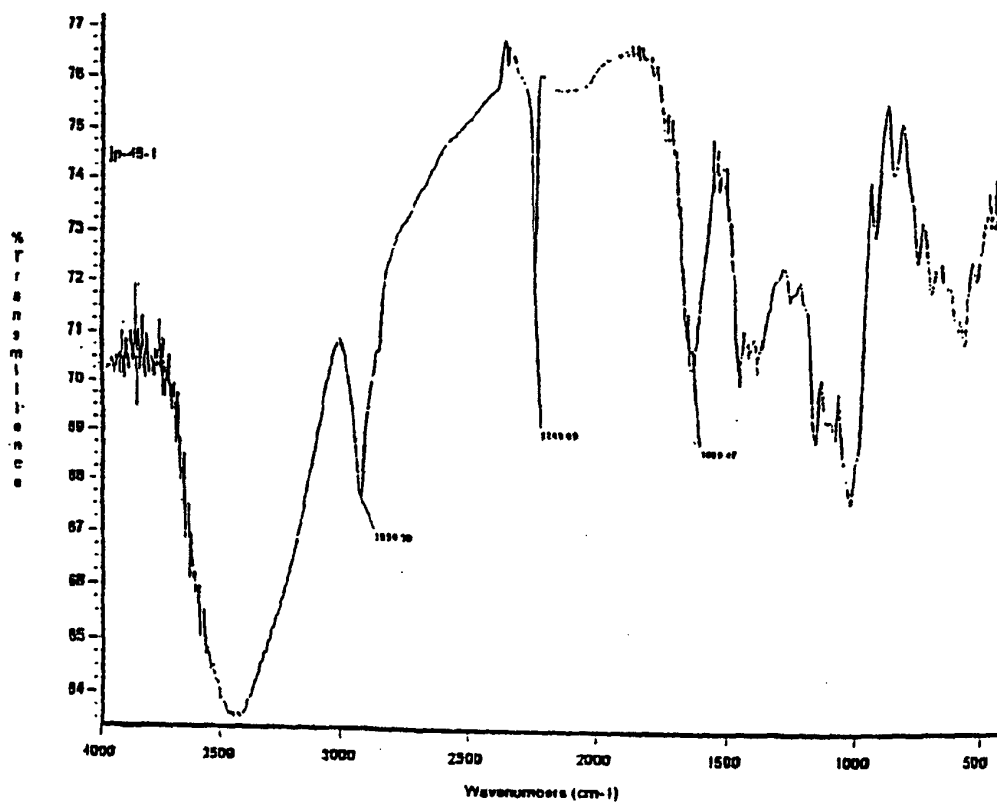


Fig. 2

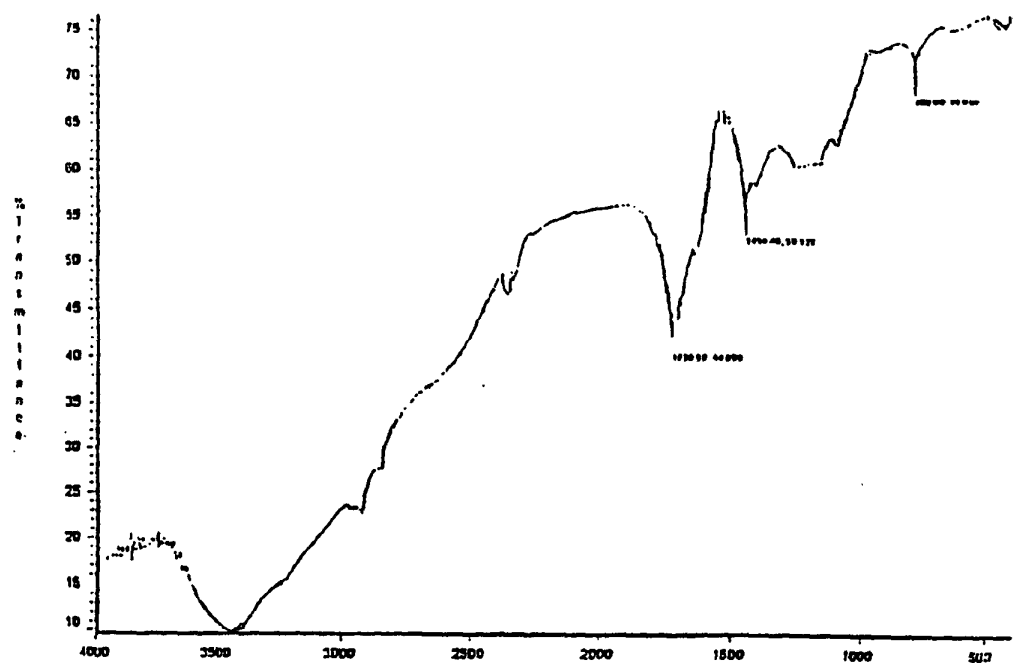


Fig. 3

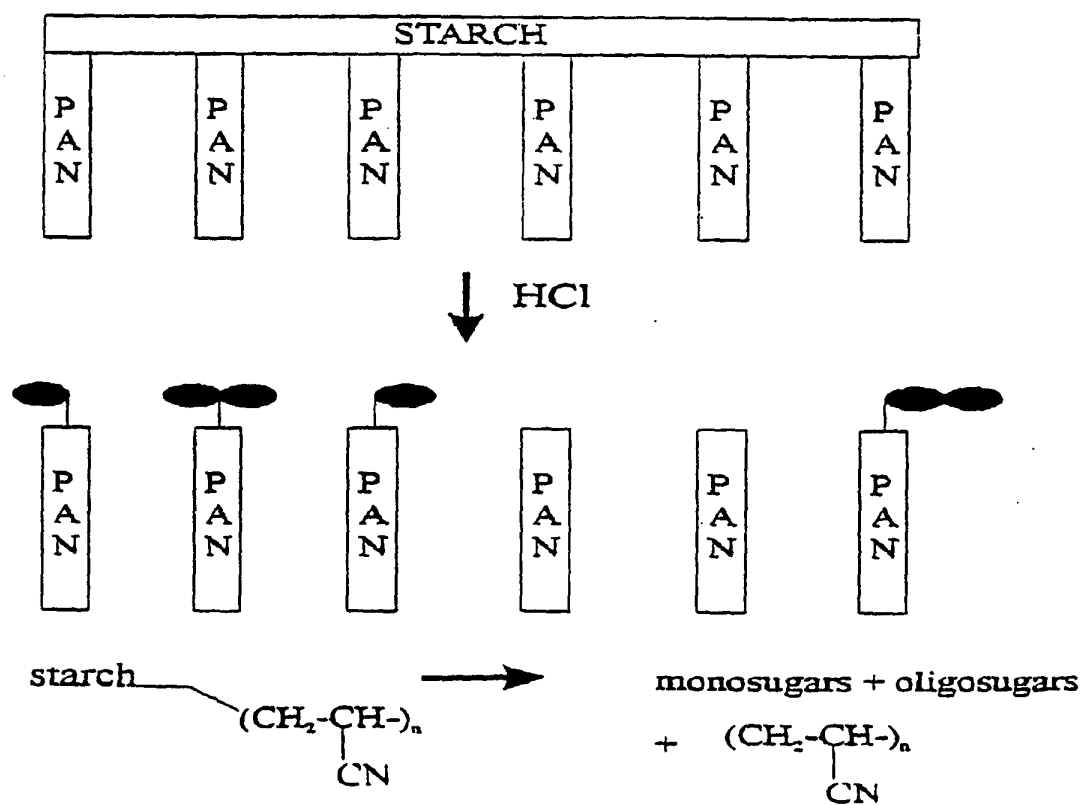


Fig. 4

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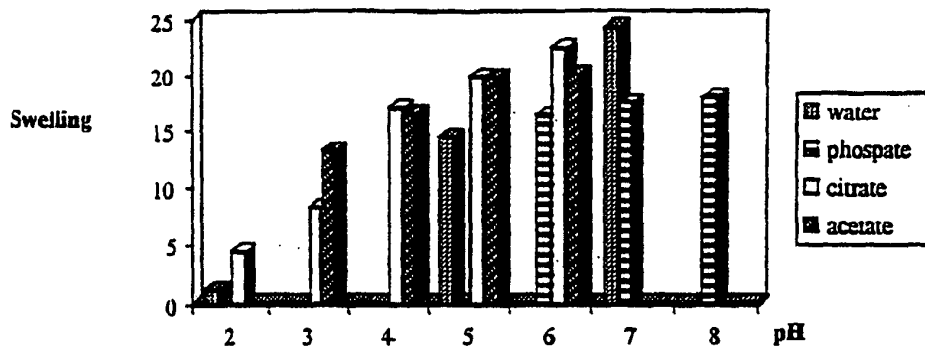


Fig. 5

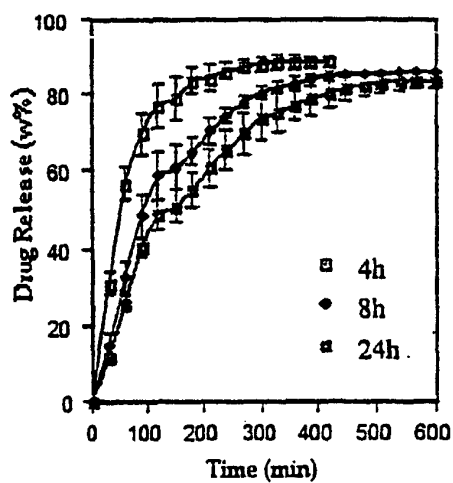


Fig. 6

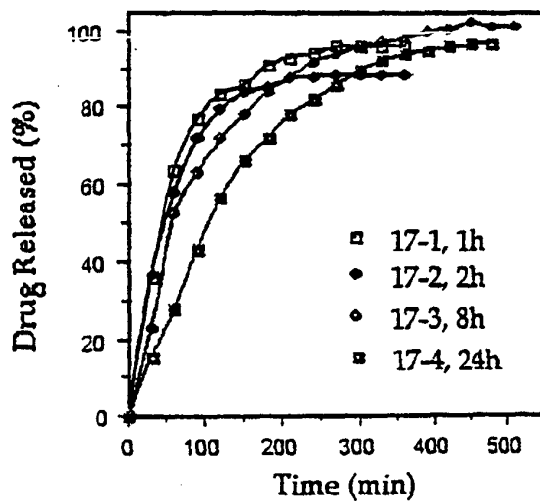


Fig. 7

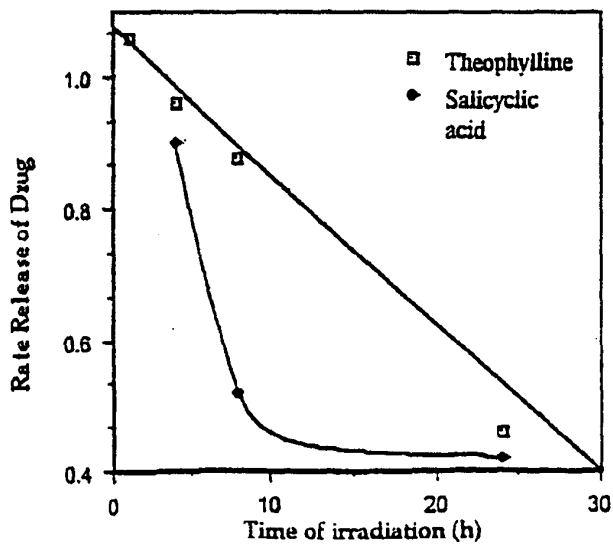


Fig. 8

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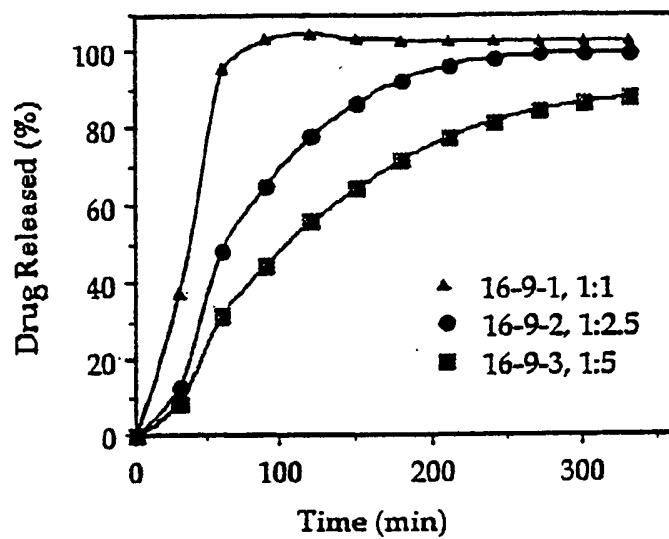


Fig. 9

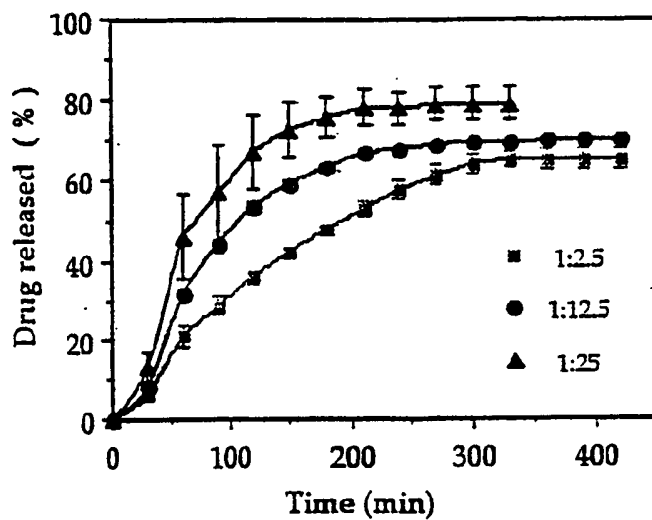


Fig. 10

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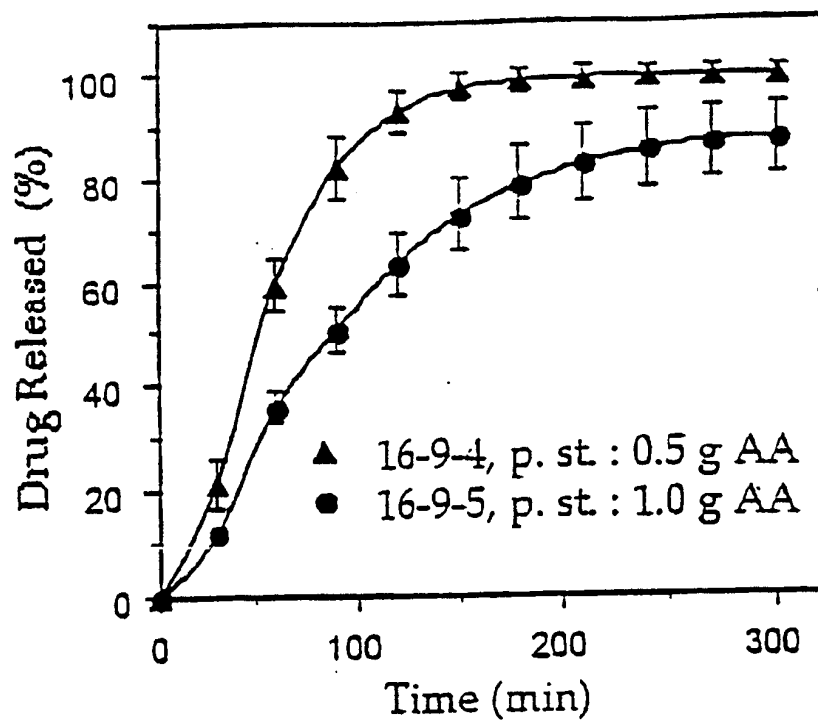


Fig. 11

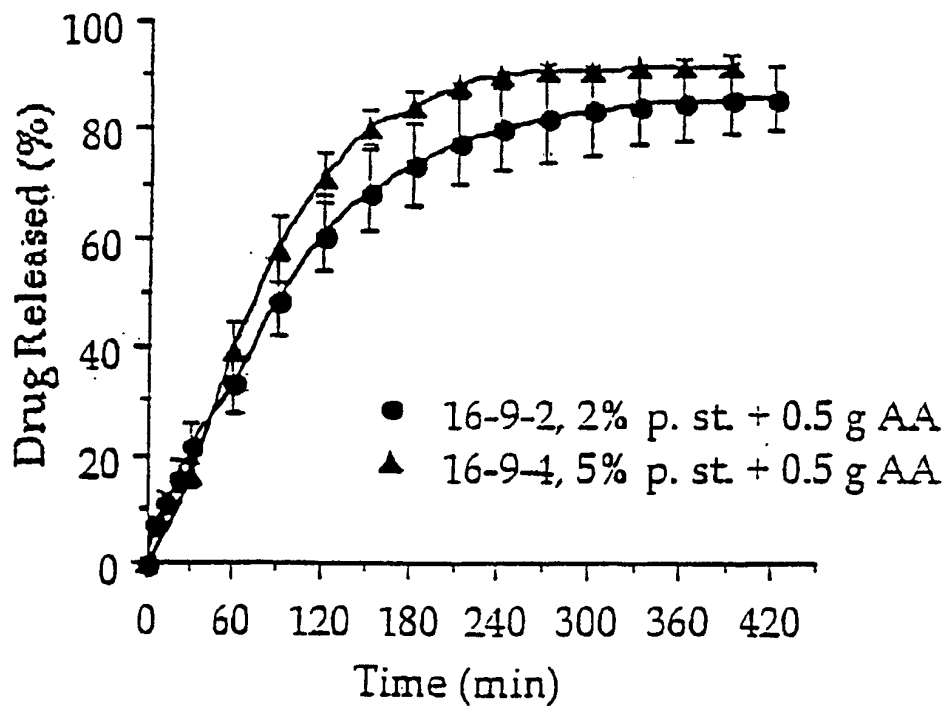


Fig. 12

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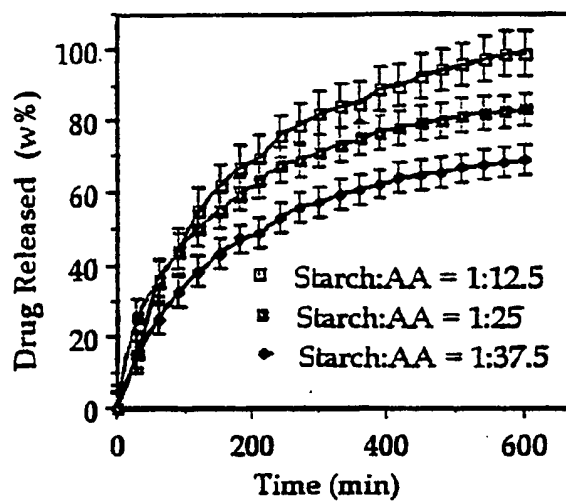


Fig. 13

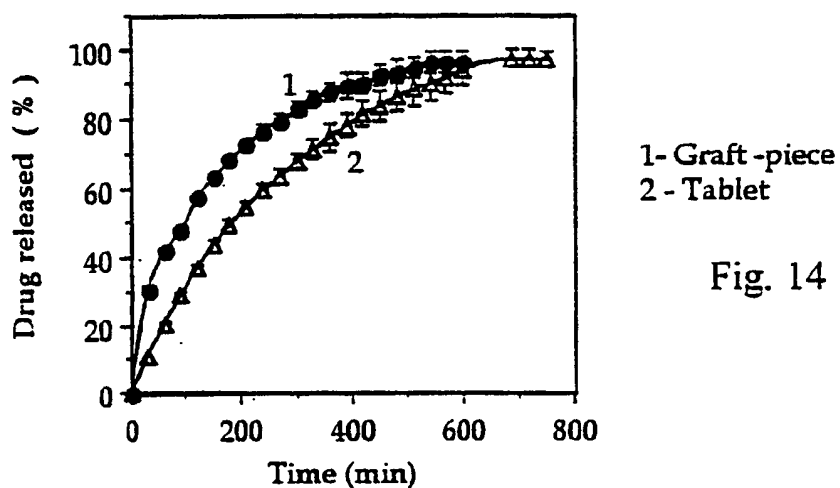


Fig. 14

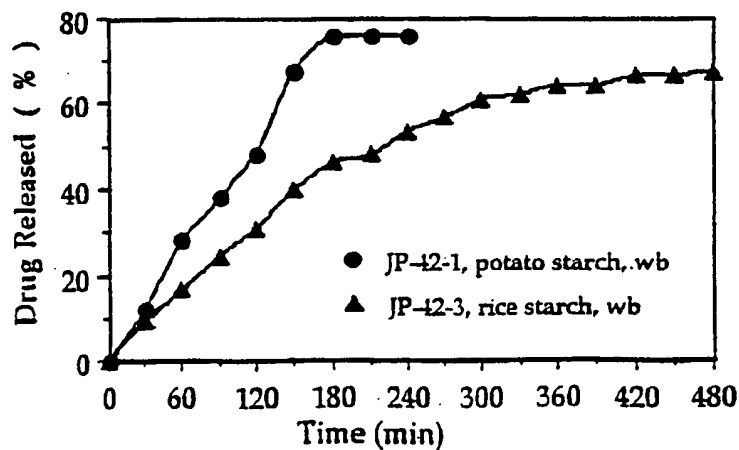


Fig. 15

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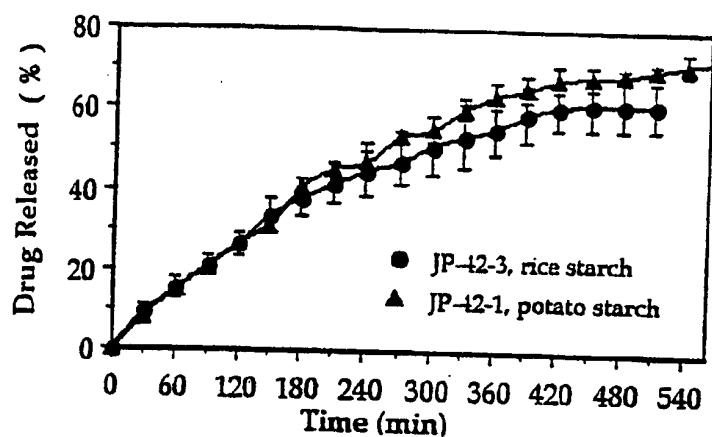


Fig. 16

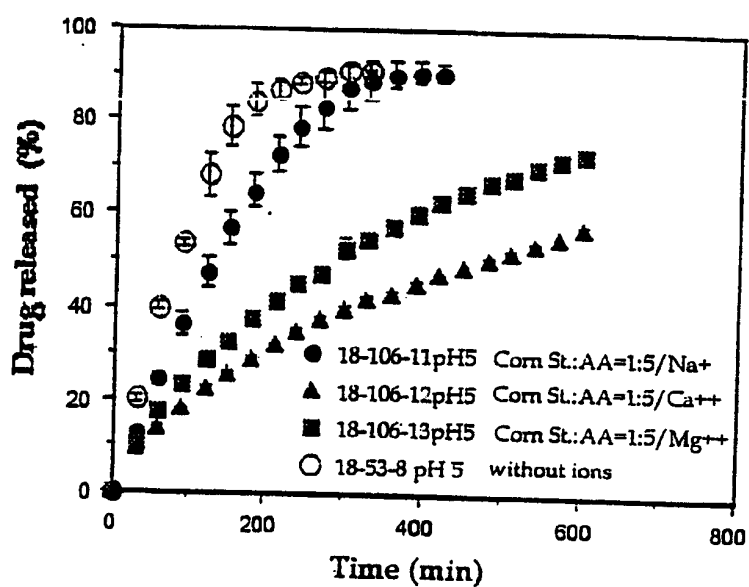


Fig. 17

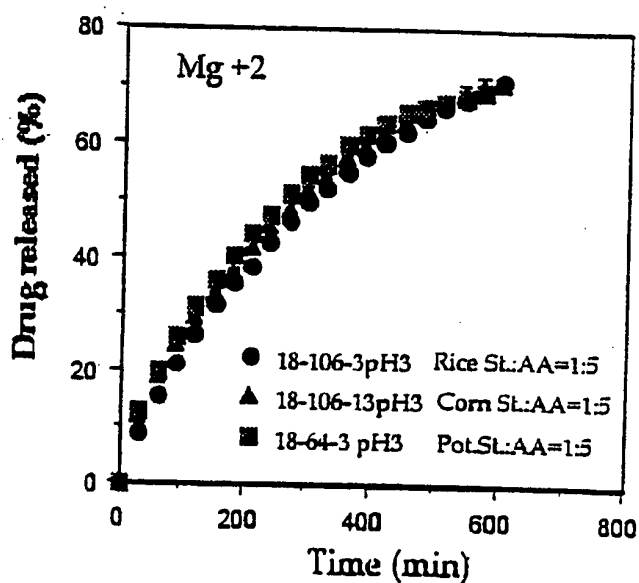


Fig. 18

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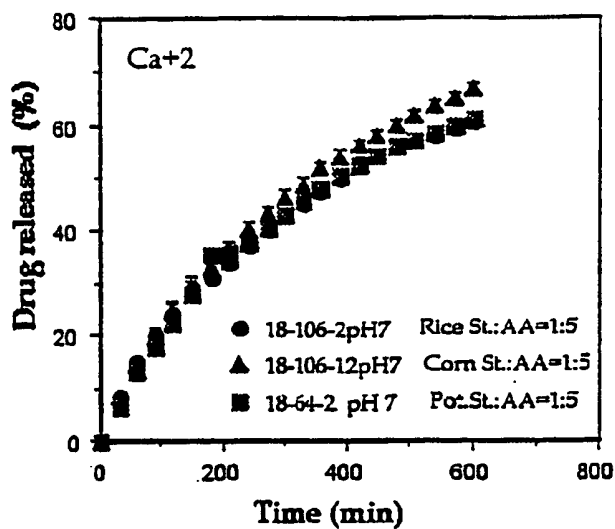


Fig. 19

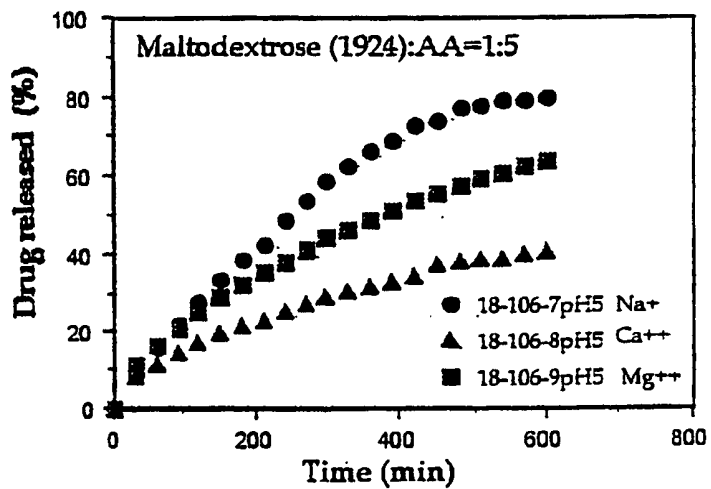


Fig. 20

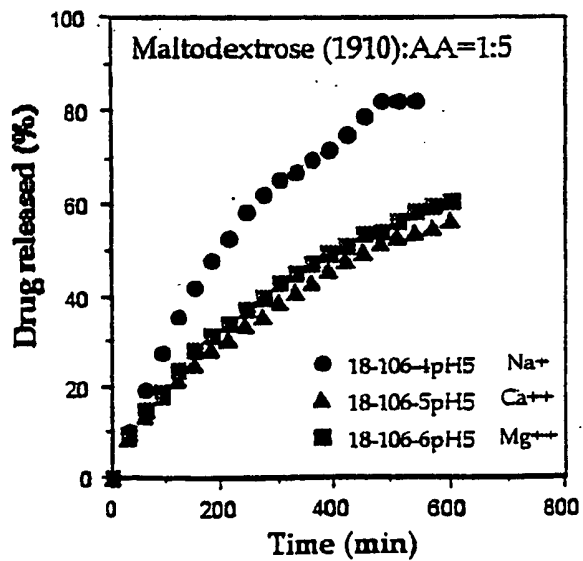


Fig. 21

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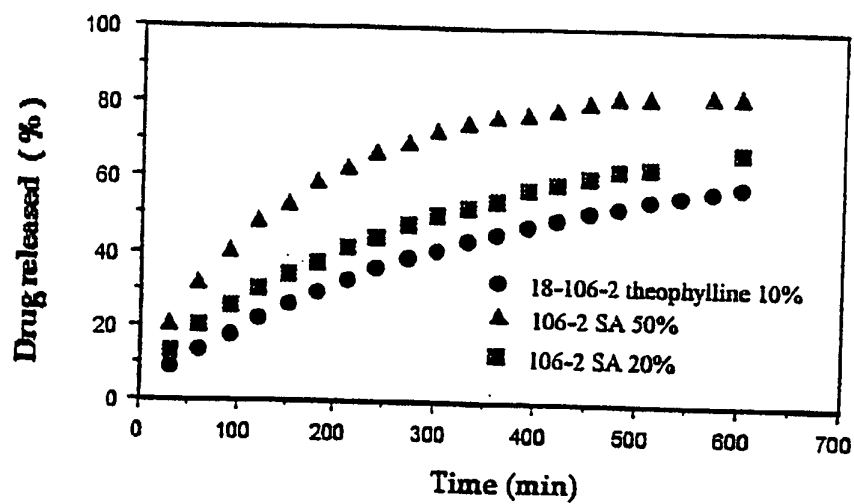


Fig. 22

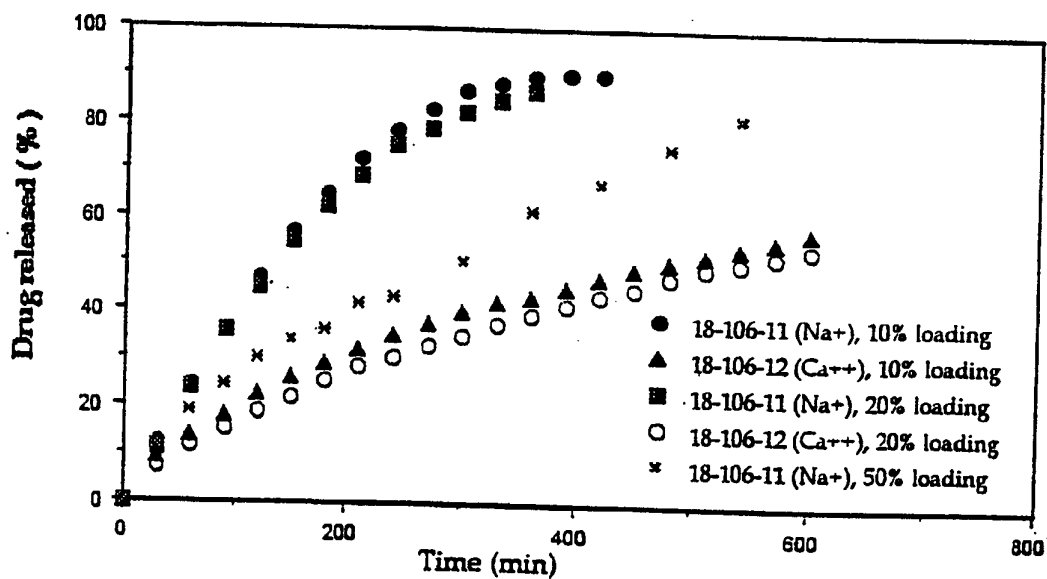
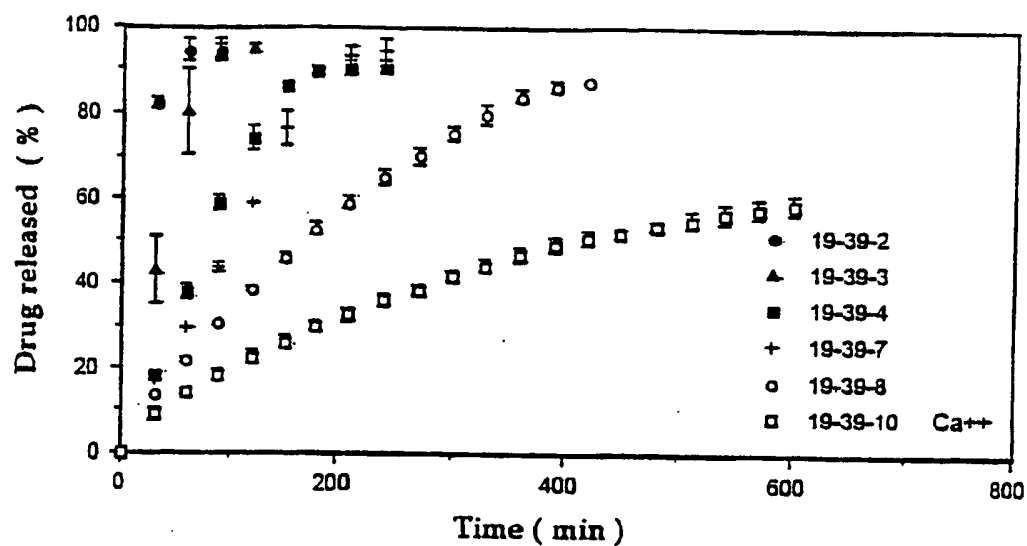


Fig. 23

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Maltodextrose (2-No 1906, 3- No 1908, 4-No 1910, 7-No 1924, 8- No 1934)

Fig. 24

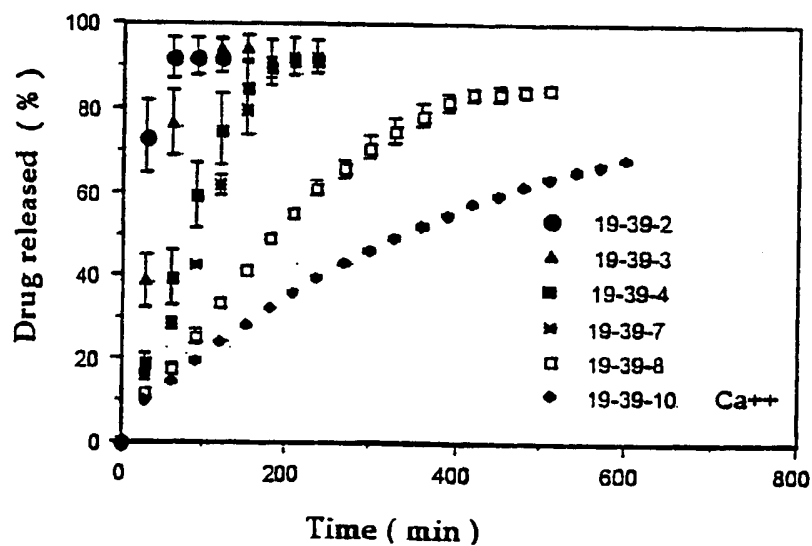


Fig. 25

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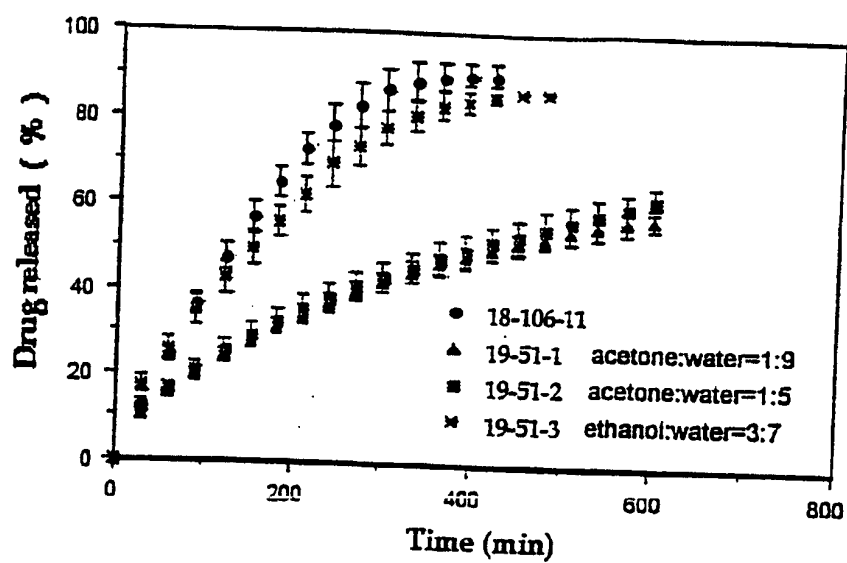


Fig. 26

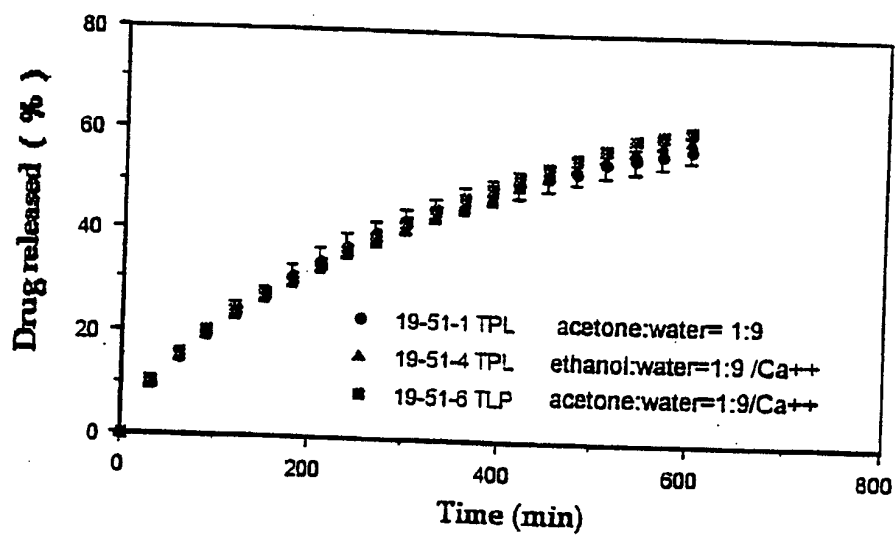


Fig. 27

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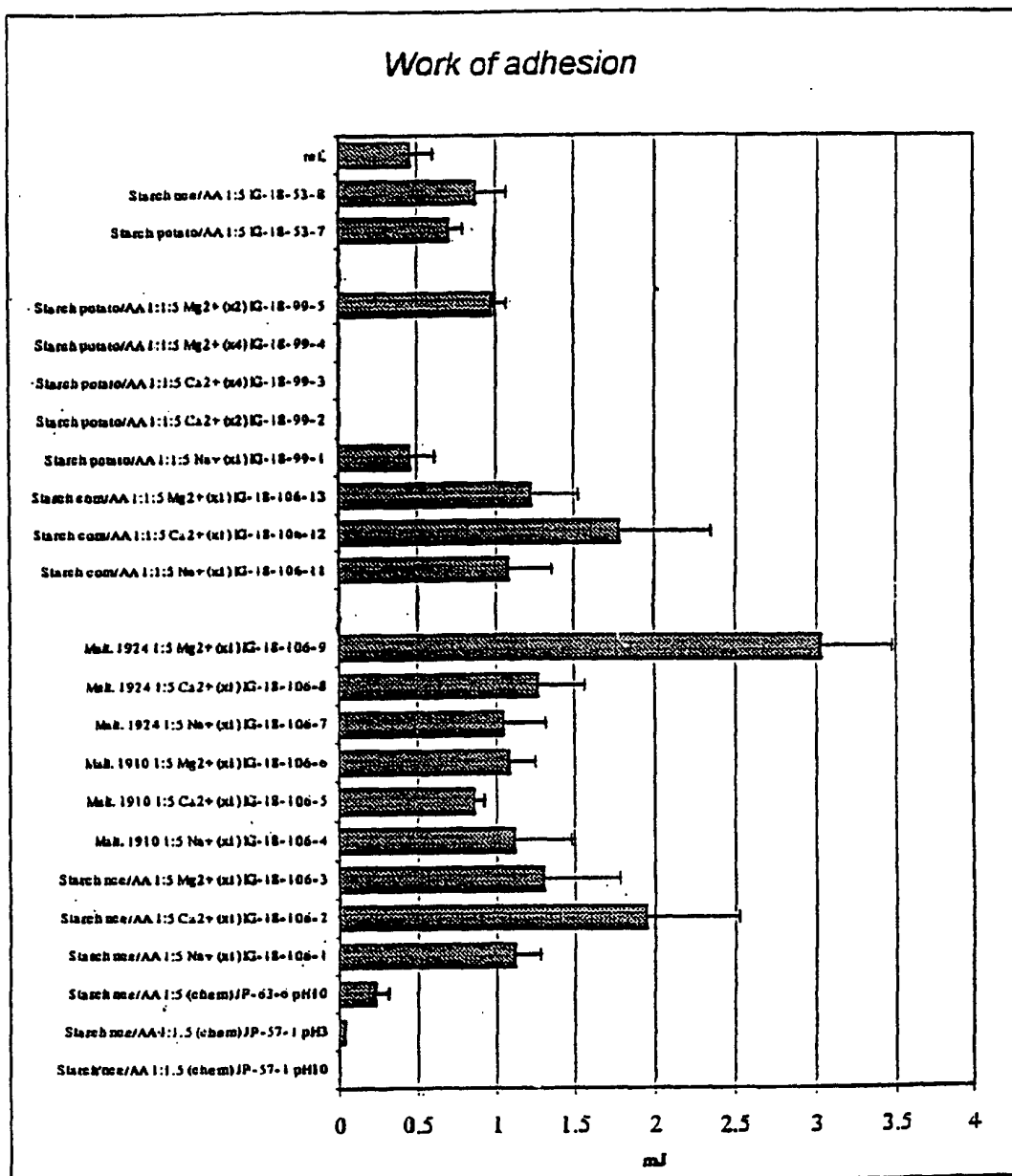


Fig. 28

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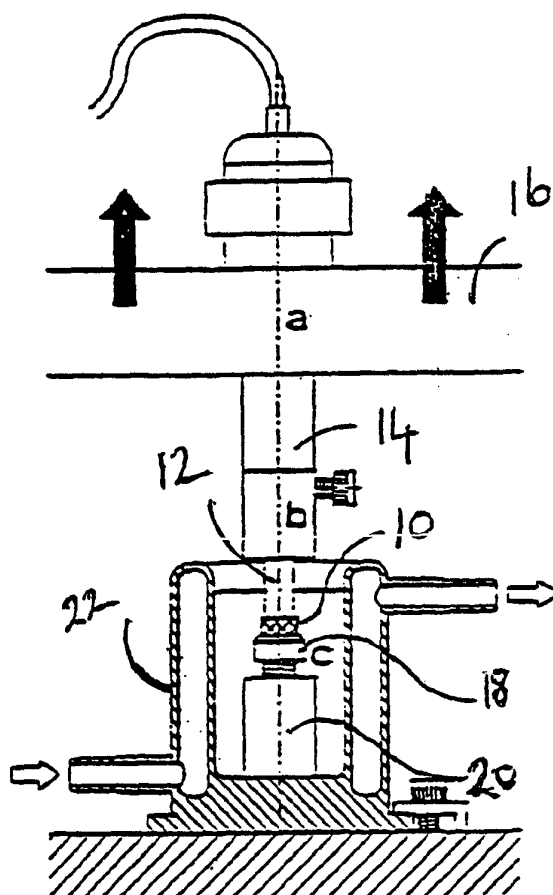


Fig. 29

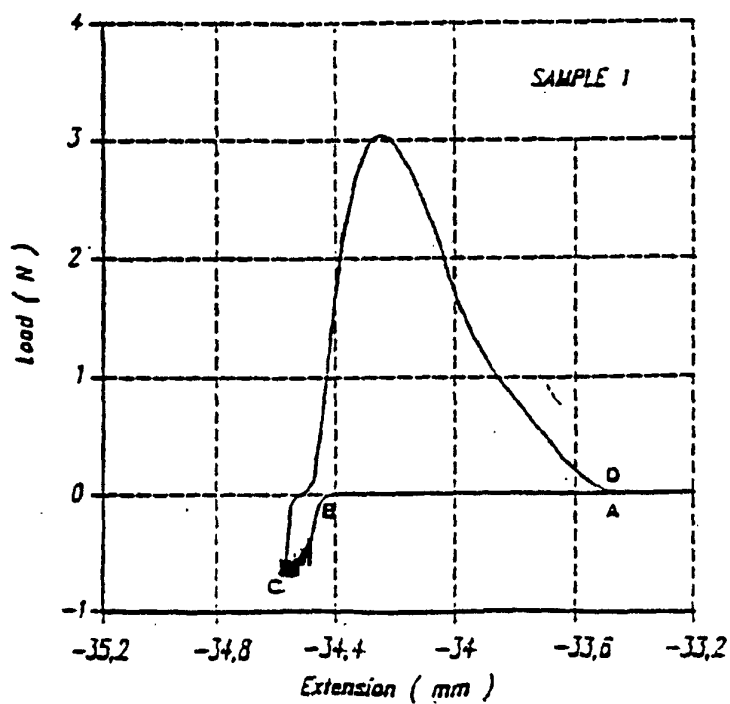


Fig. 30

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C08F251/00 C09J151/02 A61K9/20		International Application No PCT/EP 00/01107
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C08F A61K C09J		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199718 Derwent Publications Ltd., London, GB; Class A14, AN 1997-196013 XP002139142 & JP 08 291056 A (SEKISUI CHEM IND CO LTD) , 5 November 1996 (1996-11-05) abstract	1-13, 15-25
X	US 4 328 269 A (KORPMAN RALF) 4 May 1982 (1982-05-04) column 2, line 2-67; claims 1,2; examples -/--	1-4, 8-10, 15-18, 22-25
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">30 May 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">15/06/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018		Authorized officer <div style="text-align: center; font-weight: bold;">Friederich, P</div>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/01107

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 52547 A (PING HE ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 26 November 1998 (1998-11-26) page 11, line 21 -page 12, line 4; claim 1	1-25
A	US 5 804 212 A (ILLUM LISBETH) 8 September 1998 (1998-09-08) abstract column 3, line 37 - line 43	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 4328269 A	04-05-1982	NONE	
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